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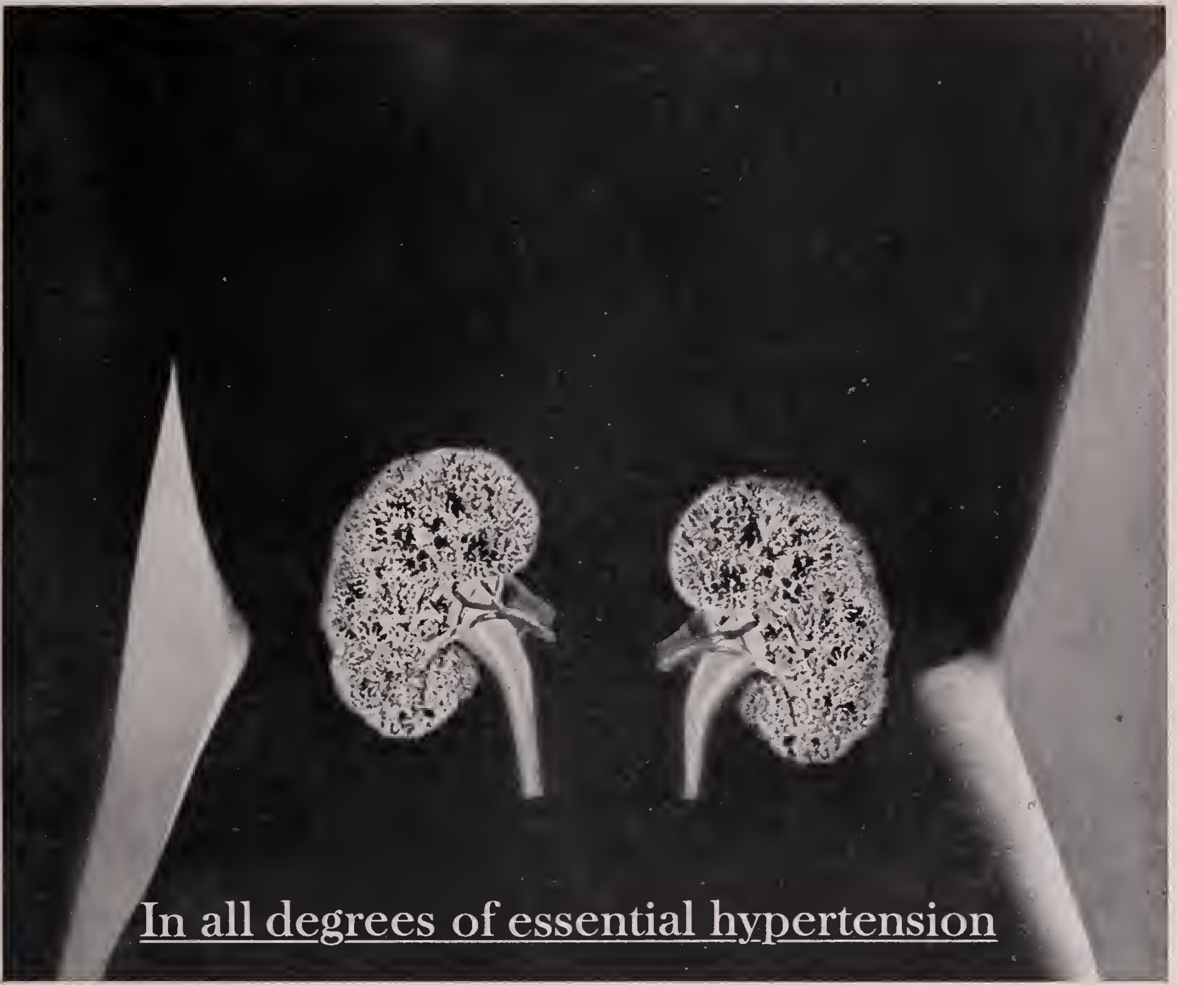

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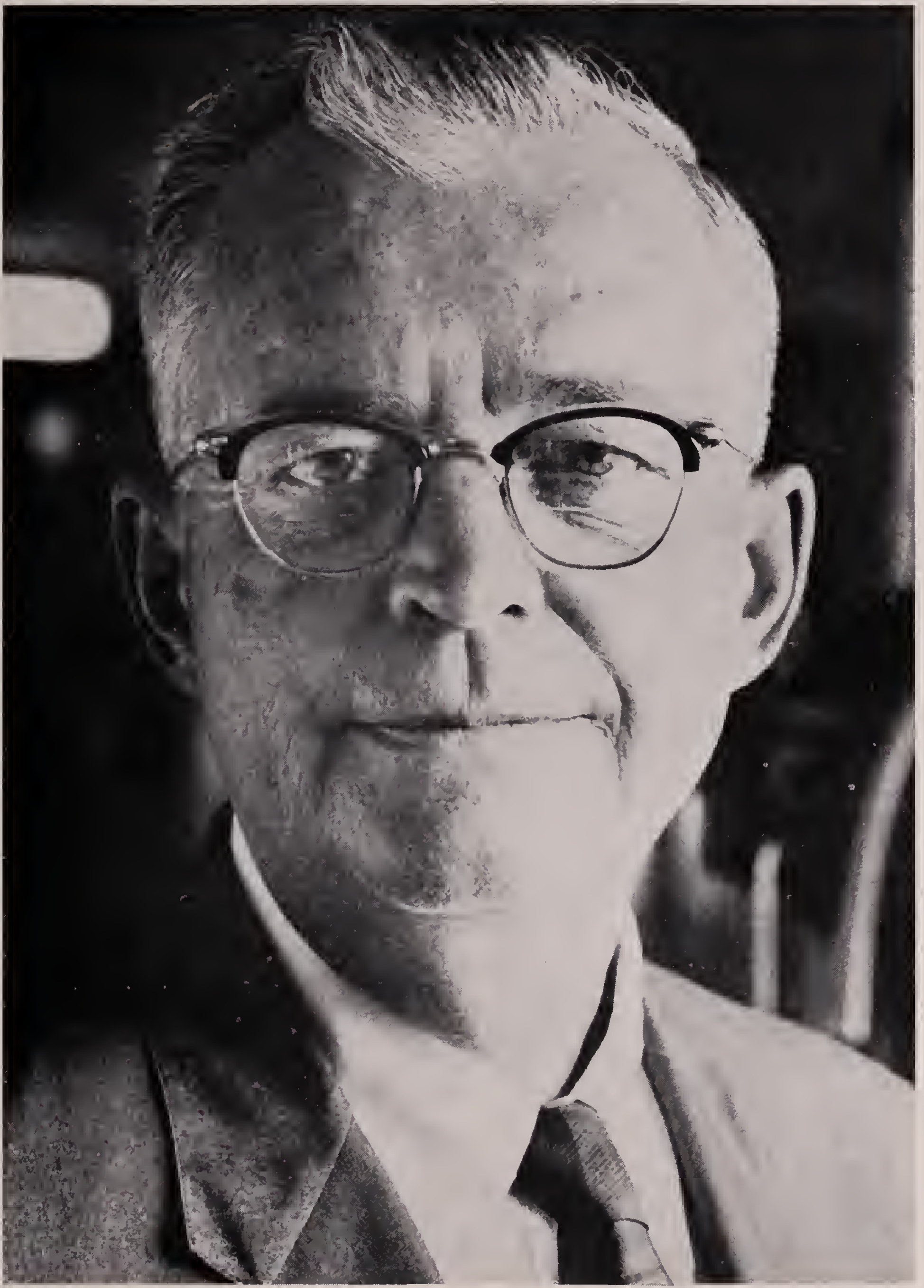

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Urinary Infections in Children*

C. D. CREEVY, M.D.**
Minneapolis, Minn.

It is well known that many factors which predispose to and excite urinary infections early in life are much commoner in the female child than in the male. It is probable that repeated and protracted fecal contamination of the external meatus of the short female urethra, particularly during the diaper age, accounts for this fact. However, this is likely to be important only in the presence of a lesion which causes stasis in some part of the urinary tract. Fecal contamination is less important in the male, although it may lead to balanoposthitis, meatitis, and hence to late meatal stricture.

Chills and fever are common in urinary infection. The location and character of pain may be difficult to identify in infants and young children, and vesical irritation is easily overlooked, particularly during the diaper age. Straining and crying during micturition may attract attention. Factors common to all pyogenic infections of the urinary tract are pyuria and bacteriuria in properly collected specimens. It is essential to realize that serious obstructive lesions with chronic infection may produce few or no subjective complaints (see case reports at end).

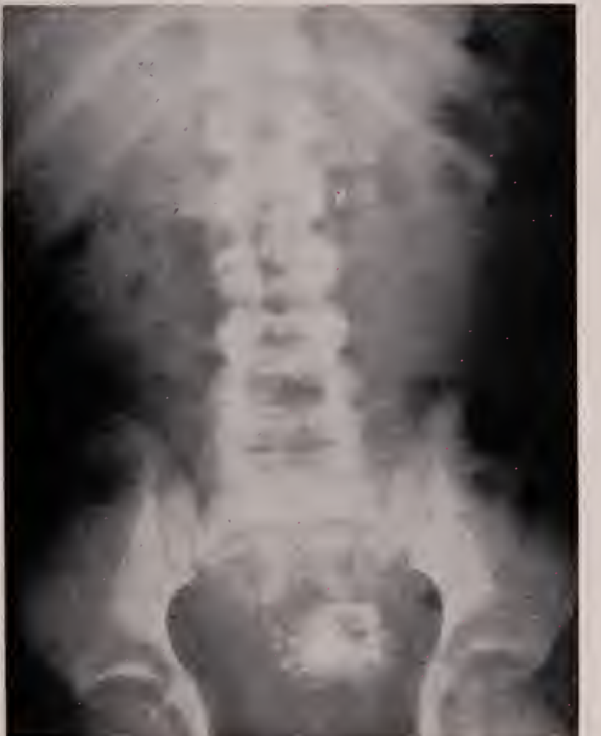

Fig. 1 — Residual lipiodol in bladder in "megacystis" syndrome.

Physical Findings

The physical examination often yields normal findings, but one should seek palpable, tender kidneys, distended bladders, tight phimoses, and strictures of the external urinary meatus. Any doubt about this last may be resolved by slipping a sterile, well-lubricated mouth thermometer through the meatus. Absence of resistance excludes a significant meatal stricture.

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*Given at the annual meeting of the Minnesota State Medical Association in Duluth on May 21, 1963.

**From the Urological Division, Department of Surgery of the Medical School, University of Minnesota, Minn.

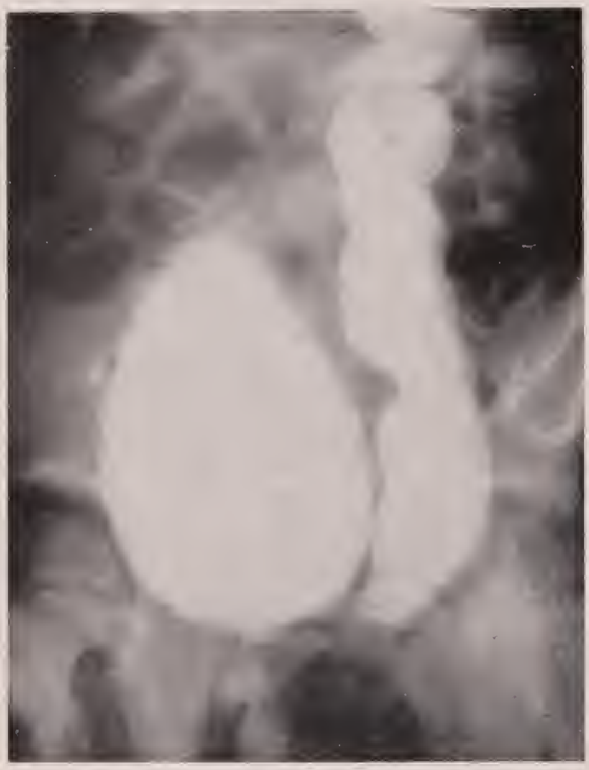

Fig. 2 — Trabeculation of the bladder due to congenital valves of prostatic urethra.

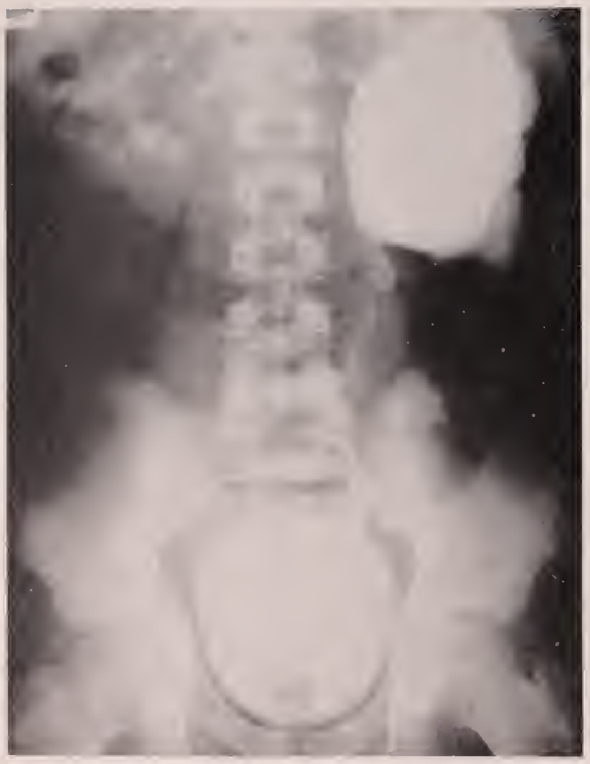

Fig. 3 — Total unilateral vesicoureteral reflux due to anomaly of intramural ureter.

Type of Urination

Perhaps the most neglected feature of the physical examination is observation of the type of urination, i.e., whether the stream starts promptly, whether it is normal in size and force, whether it is continuous or interrupted, and whether there is terminal dribbling. Because it is often inconvenient or impractical for the physician to make such observations personally, and because the testimony of parents is often unreliable, Lyon devised an apparatus for the purpose. He fastened the microphone of a tape recorder to the bottom of a metal pan which could be hung in the bowl of an ordinary toilet. The recorder was placed out of sight, and the mother was taught to operate it simply by pushing a button. It was turned on and off before and after spontaneous urination. The volume of urine was measured directly and the time consumed in passing it was measured on the tape. The normal rate ranges, with an initially full bladder, from 15 milliliters (boys) to 25 milliliters (girls) per second. One soon learns to judge the character of the stream by the sound; thus important information is secured without the inhibiting presence of a stranger, and evidence may be secured pointing to a defective detrusor or to an obstruction to urination.

Collection of the Specimen

In boys, the foreskin (if present) is retracted and the glans washed with a soap or detergent containing an antiseptic, and rinsed. After enough urine has passed to cleanse the urethra, the remainder is caught in a sterile container for microscopic examination and culture. In male infants one can tape a sterile Erlenmeyer flask to the penis.

In girls it is essential to wash and rinse the introitus thoroughly and to catch the second part of the specimen in a sterile container. When co-operation is lacking, one must use a catheter. It is difficult to imagine harm resulting from the gentle, aseptic insertion of a small, soft, sterile catheter. To discover, as one of my colleagues did, a nurse catheterizing a female who was lying in a pile of feces, explains many of the unkind things that have been said about catheters.

Indications for Investigation

Each urologist has his own views about the precise *indications for thorough investigation* of the urinary tract in the presence of pyuria, but most agree that there are four primary indications: 1. pyuria resisting for more than one week good antibacterial therapy based on cultures and, where feasible, on sensitivity tests; 2. recurrent infections (to me this means a second episode); 3. an abnormal pattern of urination; and 4. a palpable bladder or kidney. We at the University Hospital have seen too many tragedies resulting from optimistic treatment of urinary infections to adopt any less rigorous attitude.

Method of Investigation

Methods of investigation will be outlined, but no routine will be advocated because of the need to individualize, and to take into account data already secured by the physician who sends in the patient. One should, however, follow a plan which will minimize both irradiation and instrumentation. Given a patient not previously subjected to urologic study, I prefer the following sequence.

The Residual Urine

The *pattern of urination* is studied first as already outlined, since instrumentation is likely to alter it for a while. Any deviation from the normal (or a heavy chronic pyuria) requires measurement of the *residual urine.* In the co-operative patient this is perfectly simple. In the unco-operative child or in the infant, one may instill an ampoule of *ascendant lipiodol* (Young). After 24 hours of normal activity, a *KUB* is made. The presence of lipiodol, which floats on urine (Figure 1), indicates that emptying is incomplete. The KUB will also disclose the presence of stones, large kidneys, and a full bladder.

Cystourethrogram

The next step is a *cystogram* made on a film large enough to include the kidneys. With the bladder filled to tolerance, the cystogram will delineate the trabeculated bladder of obstruction or neurogenic vesical dysfunction (Figure 2), diverticula, and, not infrequently, vesicoureteral reflux (Figure 3). If this is not seen, the contrast agent is left in the bladder for 30 minutes and another film is exposed; this will often show reflux absent in the first film. If there is a question of obstruction to the outflow of urine, more contrast agent is injected into the bladder and an *oblique cystourethrogram* (Figure 4) is made during urination. This may show reflux not previously evident.

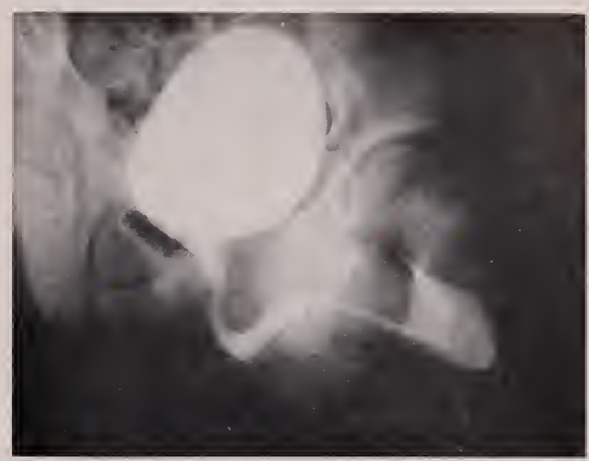

Fig. 4 — Normal voiding cystourethrogram in a boy of six years.

If the upper tract has not been well delineated by reflux, an *excretory urogram* is indicated. In those instances in which the renal outlines have not been clearly seen in the KUB, a film exposed 30 to 60 seconds after rapid injection of the contrast agent will usually opacify the renal parenchyma well enough to yield satisfactory information on this point (Figure 5).

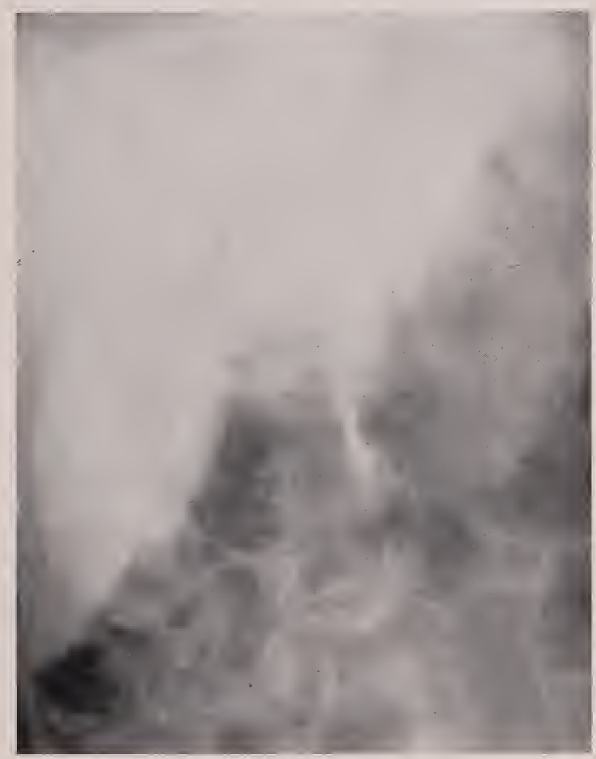

Fig. 5 — A nephrogram showing lack of circulation in the upper pole of the right kidney, due to a nonfunctioning, hydronephrotic upper segment.

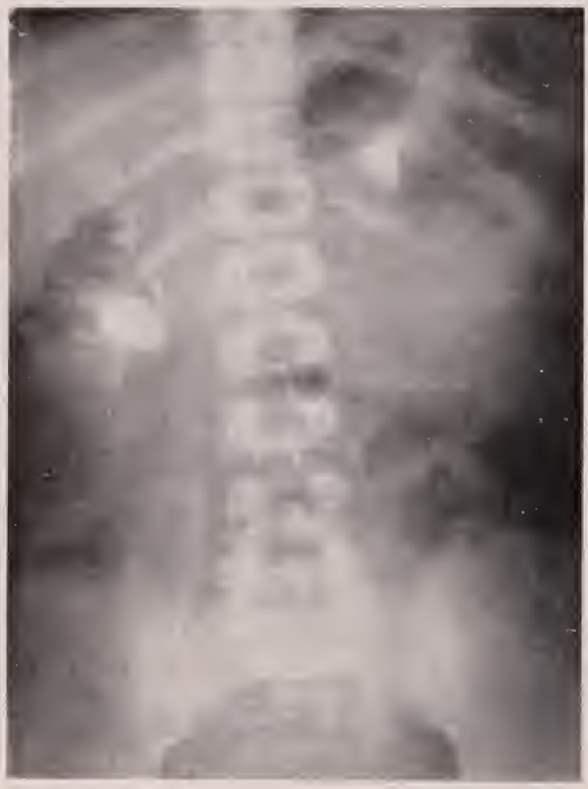

Fig. 6 — Complete bilateral duplication of renal pelves and ureters; moderate hydronephrosis and hydroureter, right lower segment; no excretion by large left lower segment.

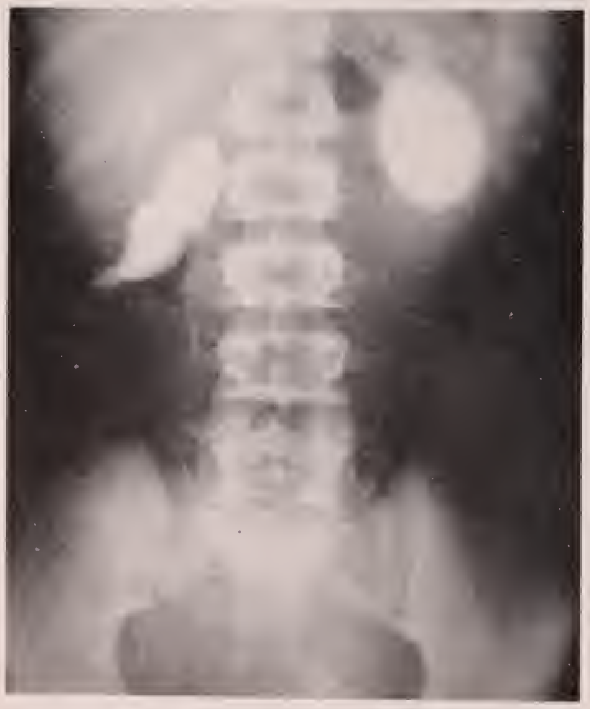

Fig. 7 — Noncalculous obstruction at right ureteropelvic junction; large stones in left kidney and ureter without excretion of contrast agent.

Films are subsequently exposed at 5, 10, and 15 or 20 minutes. Each one should be processed and inspected before the next one is exposed, in order to correct errors and to vary the technique to fit the individual circumstances.

Cystoscopy

If the measures already outlined do not yield a definitive diagnosis, *cystoscopic examination* (which includes calibration of the urethra for stricture) is now in order. Space does not permit a discussion of the numerous lesions which it may disclose.

Case Reports

Case 1

D. S., aged 13, had always been "healthy." However, his physician discovered pyuria during a respiratory infection, ordered a urogram (Figure 6), and referred him for study. The pattern of urination was normal. A cystogram was made because of the dilatation of the ureters (Figure 3); there was total reflux into the functionless lower segment on the left, and slight reflux into the lower segment on the right. The left lower segment and most of its ureter were removed, and the patient was placed on a schedule of urination by the clock to protect the other kidney. If this fails, an operation to stop reflux on the right may be necessary.

Case 2

J. L., aged 14, was seen by his family physician because of lassitude. Pyuria with B. Proteus was found and a urogram ordered (Figure 7). There was no vesicoureteral reflux. Thus far, in two sessions, the patient has had a left pelviolithotomy together with plastic widening of the ureteropelvic junction, and a left ureterolithotomy. A plastic operation will probably be needed on the right ureteropelvic junction later.

Case 3

P. O., aged 10, had had many episodes of urinary infection, each responding promptly to antibacterial therapy. Urography disclosed (Figure 8) a right hydronephrosis with bulbous dilatation of the right terminal ureter; on cinefluorography this area was aperistaltic; there was slight dilatation of the left pelvic ureter. Reflux was not found. The right pelvic ureter was detached from the bladder, narrowed, and reimplanted submucosally. A year later he is doing well with timed urination (so that the defective ureter will not have to generate high pressures to force urine into a full bladder).

Case 4

S. B., aged 6 months, became profoundly ill with chills, fever, a distended bladder, and uremia. A cystogram ordered by her physician (Figure 9) showed a large ureterocele. Procedures employed so far have in-

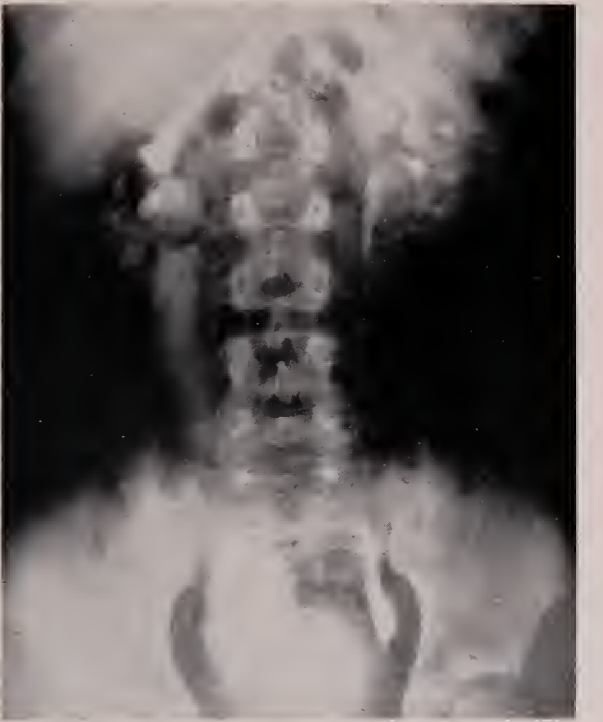

Fig. 8 — Congenital ureterectasis, advanced on right, minimal on left, with aperistaltic terminal segment on right. No reflux.

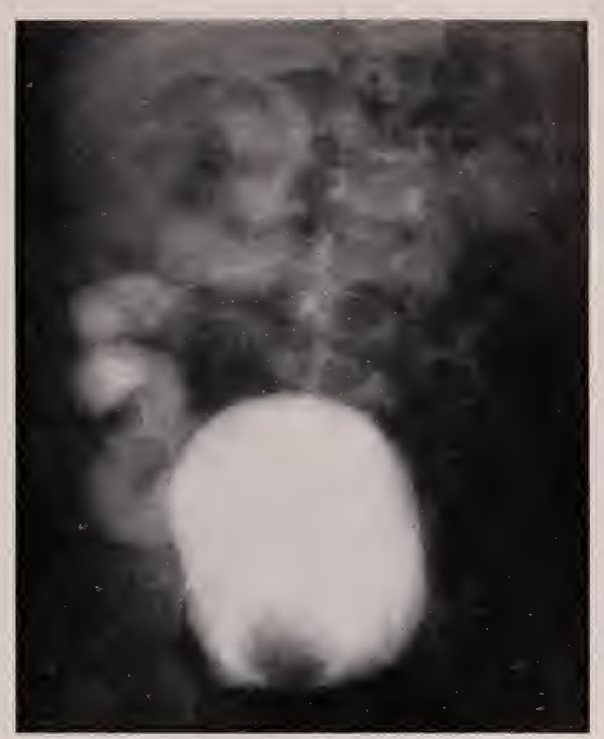

Fig. 9 — A large ureterocele in a girl of six months. This had destroyed the duplicated right upper urinary tract, and had caused severe dilatation on the left.

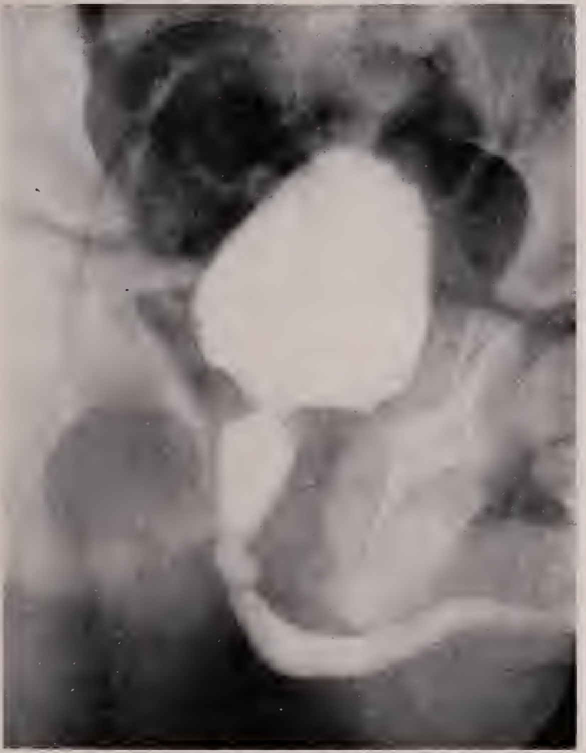

Fig. 10 — An urethrogram showing the typical dilatation of the prostatic urethra due to congenital mucosal valves, with but little obstruction.

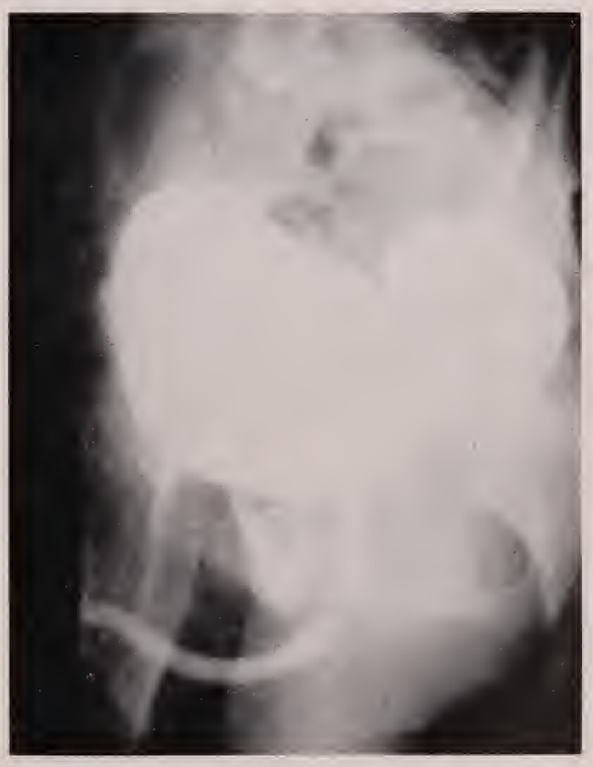

Fig. 11 — A vesical diverticulum in a boy of 10 has compressed the only ureter.

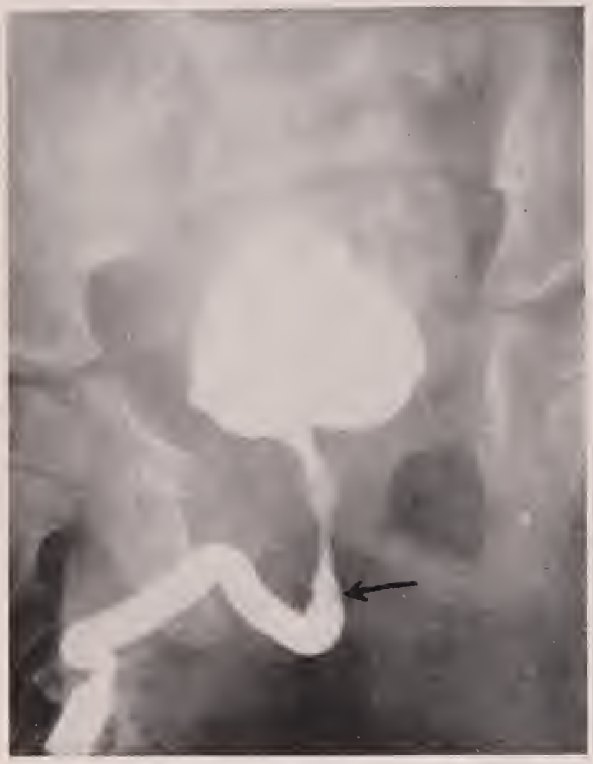

Fig. 12 — A soft stricture has caused very severe damage to the upper urinary tract through parental neglect.

cluded: excision of the ureterocele, right heminephroureterectomy, replacement of the failing left ureter by ileum, and transurethral resection. The end result, because of preoperative damage to the left kidney, is still in doubt, although she is currently well.

Case 5

G. M., aged 5, had difficult urination pyuria, and nocturnal as well as diurnal enuresis. The upper urinary tract was normal; reflux was absent, and the voiding cystourethrogram showed the dilated prostatic urethra attributed by Hamm and Waterhouse to congenital mucosal valves (Figure 10). They were destroyed by electrocoagulation with a good immediate result. Rarely are such valves found before the upper tract has been damaged. The degree of obstruction was minor.

Case 6

M. H., aged 10, had been regarded as the healthiest member of a family of seven children until he developed a urinary infection. When it failed to subside promptly, his physician ordered a urogram and was horrified to observe a large, poorly functioning, solitary left kidney with a much dilated ureter. A voiding cystourethrogram at the University Hospital (Figure 11) showed a large diverticulum of the bladder without vesicoureteral reflux. Cystoscopy verified the suspicion that the left ureter emptied into it. Evidently the diverticulum, which has a small mouth, compresses the ureter and is responsible for the severe dilatation of the pelvis and ureter. Treatment will consist of excision of the diverticulum and oblique reimplantation of the ureter.

Case 7

R. J., aged 4, was a badly neglected member of a large family. He was taken to a physician only when he developed a severe urinary infection; he was promptly referred to the University Hospital, where he was found to have advanced bilateral hydronephroses and hydroureters due to a soft stricture of the bulbous urethra (Figure 12). Ileac diversion of the urine (Bricker's operation) was finally required. He is doing well several years later.

Summary and Conclusions

1. Pyuria in a properly collected specimen from an infant or child is serious until the contrary has been proved.

2. Failure to achieve definitive cure within a week, a single recurrence after apparent cure, or an abnormal pattern of voiding demand careful study of the urinary tract.

3. Advanced damage to the urinary tract may occur with few or no symptoms if urinary stasis exists.

4. Seven abbreviated case reports support these opinions.

VICTOR HORSLEY'S SIGN

(Middle meningeal hemorrhage)

This sign is manifested by a difference in the axillary temperature from one side to the other. In advanced cases of middle meningeal hemorrhage there is often an increase in the temperature on the paralyzed side, as compared to the contralateral side.

Rearrange Your Prejudices

It is well for people who think to change their minds occasionally in order to keep them clean. For those who do not think, it is best at least to rearrange their prejudices once in a while.—Luther Burbank

Catastrophic Rupture

• of • the • Gravid • Uterus

RAYMOND A. LEE, M.D.*
REGINALD A. SMITH, M.D.**
RICHARD E. SYMMONDS, M.D.†
Rochester, Minn.

Few obstetric emergencies produce as much maternal morbidity and fetal loss as does rupture of the gravid uterus. During the 28-year interval from 1935 through 1962, in an obstetric practice of 36,189 cases, 13 patients suffered complete rupture of the pregnant uterus — an incidence of one ruptured uterus in 2784 obstetric cases. Of these, five occurred during difficult breech deliveries and five followed previous low cesarean sections. One uterus ruptured during a high forceps delivery accomplished for prolapse of an umbilical cord; another ruptured during induction of labor with intravenously administered dilute oxytocin (Pitocin) solution; and a third occurred at the site of implantation of a Fallopian tube during pregnancy after operation for correction of tubal occlusion.

Clinical Picture

Regardless of the etiology of rupture, the clinical picture of the condition was relatively constant. If the patient was conscious, the uterus and lower part of the abdomen were noted to be painful, tender, and tense, and there was vaginal bleeding of varying intensity. Shock became manifest either gradually or rapidly, depending on the amount of blood lost. If the infant had been extruded from the uterus into the peritoneal cavity, fetal parts could be palpated immediately beneath the abdominal wall. Fetal movement and heart rate gradually disappeared. The uterus usually contracted to approximately the size it would be after four months of pregnancy. If analgesics or anesthesia had been administered, recognition of the condition was at times delayed.

Management

Once uterine rupture was recognized, management consisted of prompt and sufficient blood replacement and appropriate surgical intervention. The common tendency to underestimate the blood loss in many obstetric problems should be recognized. Immediate laparotomy must be undertaken, preferably before the appearance of clinical signs of shock. The surgical procedure accomplished must be individualized and depends on the extent and location of the lacera-

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TABLE

Summary of Histories in Cases of Catastrophic Rupture of the Gravid Uterus

Case	Age, Year	Gravida / Parity	Etiology	Time of Rupture	Treatment*	Outcome of Fetus	Outcome of Mother
1	33	2/1	Rupture of old cesarean scar	36 weeks	(1) 3000 ml. whole blood (2) TAH after vaginal delivery	Stillborn	Lived
2	28	2/1	Rupture of old cesarean scar	38 weeks	(1) 2500 ml. whole blood (2) TAH after vaginal delivery	Stillborn	Lived
3	33	5/4	Rupture of old cesarean scar	38 weeks	(1) 4500 ml. whole blood (2) TAH	Stillborn	Lived
4	39	2/1	Rupture of old cesarean	38 weeks	(1) 2000 ml. whole blood (2) TAH	Stillborn	Lived
5	36	5/3	Rupture of old cesarean scar	36 weeks	(1) 1000 ml. whole blood (2) Repair of rupture	Stillborn	Lived
6	32	2/0	Rupture at site of implanted Fallopian tube	33 weeks	(1) 1000 ml. whole blood (2) Repair of rupture	Neonatal death	Lived
7	22	4/3	I.v. oxytocin induction, postmaturity	43 weeks	(1) 2500 ml. whole blood (2) TAH	Stillborn	Lived
8	29	2/1	Prolapsed cord, high forceps	Term	(1) 5500 ml. whole blood (2) TAH	Lived	Lived
9	30	3/2	Transverse lie version, breech extraction, Piper forceps	Term	(1) 1500 ml. whole blood (2) TAH	Lived	Lived
10	26	8/7	Breech extraction, Piper forceps	Term	(1) 4500 ml. whole blood (2) TAH	Lived	Lived
11	44	9/8	Breech extraction, Piper forceps	Term	(1) 2000 ml. whole blood (2) TAH	Lived	Lived
12	29	3/2	Breech extraction	Term	(1) 1500 ml. whole blood (2) TAH	Lived	Lived
13	34	9/8	Transverse lie version, breech extraction	Term	(1) 1000 ml. whole blood (2) TAH	Lived	Lived

*TAH denotes total abdominal hysterectomy.

tion and on the condition, age and parity of the patient. In 11 of our patients, total abdominal hysterectomy was performed.

Since all of the mothers survived, one cannot criticize the operative management. Nevertheless, it should be emphasized that there is good reason to use subtotal hysterectomy in these critically ill patients. When the laceration does not involve the cervix, and the patient's condition is precarious, subtotal hysterectomy can be accomplished with greater rapidity, with less blood loss, and with equally effective control of hemorrhage from the ruptured fundus.

Freshening a ruptured cesarean scar and reclosure of the wound in the uterus was possible in only two of the patients. All uterine ruptures in this series were of catastrophic degree, associated with intra-abdominal hemorrhage, pain, and shock. The management of silent rupture of the uterus with dehiscence of a previous scar, found only at the time of subsequent cesarean section, is not considered in this report.

Spontaneous rupture of the uterus following a previous cesarean section contributed five of our fetal losses. One occurred after induction of labor with intravenously administered dilute oxytocin solution. Another occurred as a result of rupture and extrusion of the placenta through the site of previous surgical implantation of a uterine tube. Living infants were obtained in each of the six cases of uterine rupture following operative vaginal delivery. Since rupture occurred during the course of the procedure in each instance, the infant was delivered before untoward effects of the rupture could affect its well-being.

There were no maternal deaths in the series. The histories of the patients suffering from rupture of the gravid uterus are presented in summary in the accompanying table.

Comment

In consideration of the cases in which rupture of the scar of a previous cesarean section occurred, it is noted that the time of spontaneous rupture was from two to four weeks prior to the expected time of confinement. In only two of the cases did rupture of the uterine scar occur following the onset of labor. Tenderness of the scar was not a prominent feature before the rupture. In our experience, this classical sign has been rather unreliable in that it has been much more prominent in other patients in whom subsequent cesarean section showed that the previous scar was intact. There seems to be no characteristic sign or finding to allow detection of impending rupture of the uterine scar.

In retrospect it has been noted that, in the majority of our cases of uterine rupture associated with difficult breech delivery, there was an unrecognized degree of cephalopelvic disproportion present. Cesarean section should have been the method of choice of delivery in this group of patients. When applying the procedure of internal version or forceps delivery of the aftercoming head, manual exploration of the uterine cavity for laceration is definitely indicated. Lacerated uteri will then be recognized early. Similarly, with delivery of infants from the vertex position when high forceps applications are necessary, or with a delivery from below after previous cesarean section, manual exploration of the uterine cavity is also strongly advised.

Summary

Early recognition of uterine rupture, adequate and immediate blood replacement, and proper surgical intervention are the basic principles in the management of this catastrophic condition.

Self Discipline

Since the days of Pythagoras it has been recognized that a world of law implies a life of self-discipline if that life is to reach its highest development. Thus in an era when many old conventions become outworn, the clear teaching of science is of especial value: If man will learn the truth and abide by it, that truth will make him free.—Arthur H. Compton

Moses the Father of Preventive Medicine

In antiquity, as in all ages, good health was a highly prized possession. Hard physical work was required of everyone in the nomadic and agricultural society of the ancient Hebrews. Without good health a person could not share fully in the life of his community. He was in danger of becoming an outcast. Good health was looked upon as a gift of God. The Hebrew word *shalem* — "healthy" or "whole" — is a cognate of *shalom* — "peace." Soundness of body and peace of mind were intimately associated. They were equally gifts of God to his people. A summary of the qualities of the ideally healthy man is found in the description of King David, "who is skillful in playing, a man of valor, a man of war, prudent in speech, and of a good presence; and the Lord is with him." (I Sam. 16:18). The outcome of good health is longevity, and the great men of the past who stood in the unique favor of God were inevitably rewarded with long life. Yet even in this hope the ancient Hebrews were not unaware of the medical problems which faced the aged. "The years of our life are threescore and ten, or even by reason of strength fourscore; yet their span is toil and trouble;. . ." (Ps. 90:10).

Despite the high value the ancient Hebrews placed upon health their knowledge of curative medicine was extremely limited. In the earliest phases of Hebrew thought illness was looked upon as a divine judgment of sin. Although this essentially penal theory of disease was criticized and reformulated by later thinkers, it remained the dominant popular view. Only the exceptional individual in the Old Testament consulted a physician. When King Asa suffered an acute illness two years before his death he called in a physician. Of this action the writer of Chronicles spoke in the most negative terms: "yet even in his disease he did not seek the Lord, but sought help from physicians." (II Chr. 16:12). The prophets at times gave medical advice and made prognoses. Isaiah directed a cake of figs to be applied to a boil from which King Hezekiah suffered. (Is. 38:21). The prophet had at one time warned Hezekiah that his death was imminent, yet after the king repented he changed his prognosis, giving the king fifteen more years of life. But this extention of life was clearly related to the king's repentence, not to the use of any curative technique. The poultice of figs was applied only after the king had been assured of longer life. It did not stand in a causal relation to his recovery. (Compare Is. 38:1–5 and 38:21). Since God is the great Physician of his people, his forgiveness, not any human action, brings health to the ill person. Hence, the real forward thrust of Old Testament culture was not in curative medicine. Its unique contribution was in preventive medicine and social hygiene. *(Continued next month)*

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Rocking Chair

Worry is like a rocking chair — gives you something to do, but doesn't get you anywhere.

Familial Sarcoidosis

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THE FIRST case of sarcoidosis was reported by J. Hutchinson in 1869, and the histological picture of the lesions was first described by Boeck in 1899. Later, Besnier described the cutaneous manifestations of the disease as Lupus Pernios, and Heerfordt described it as uveparotid fever, which twenty-five years later was recognized as sarcoidosis. The literature related to this disease has greatly increased in recent years, and in order to avoid confusion in the diagnosis, it has become necessary to define the disease as proposed by the National Research Council in 1948.[1] Israel and associates[2] have outlined the diagnostic criteria as follows: a) anatomic pathological confirmation by biopsy, b) a consistent clinical picture, and c) the exclusion of any other disease which can give a similar clinical picture (particularly tuberculosis).

The etiology and pathogenesis of sarcoidosis remains obscure at the present time. A tuberculous etiology is strongly supported by reports in the British[3] and Scandinavian[4] literature. On the other hand, Jaques[5] and Kass[6] suggested that sarcoidosis may be due to an abnormal reaction of the organism to antigenic stimuli. The search for a causative antigen has been studied more extensively since Cummings[8] pointed out a correlation between the birthplace of patients with sarcoidosis and the pine forest areas of the United States. This geographic distribution has also been confirmed in Sweden by Wallgren.[9]

There are only 33 cases of familial sarcoidosis[10-11] reported in the world literature. Many of these do not fulfill the above mentioned diagnostic criteria, but we will not attempt to evaluate the accuracy of the diagnosis of those cases. Of the familial cases reported to date, twenty-one have been described in nontwin siblings, six cases in twins and six cases in parent-offspring relationships. Of the nontwin cases, nine have been reported in the American literature. Only three documented cases have been described with more than two members of the family involved.

The purpose of this paper is to present the occurrence of sarcoidosis in two nontwin siblings who have a common environmental origin in pine-forested areas, with brief mention of the possible etiology in these cases.

Case Reports

Case 1

A 48-year-old negro male was admitted to Mount Sinai Hospital on August 15, 1960, complaining of pleuritic pain in the left chest region of two days' duration. For three days prior to admission, he had been febrile and had had a cough, productive of yellowish sputum. He had been bothered by "frequent colds" for the previous several years since moving to Minneapolis from Alabama. His last hospital admission had

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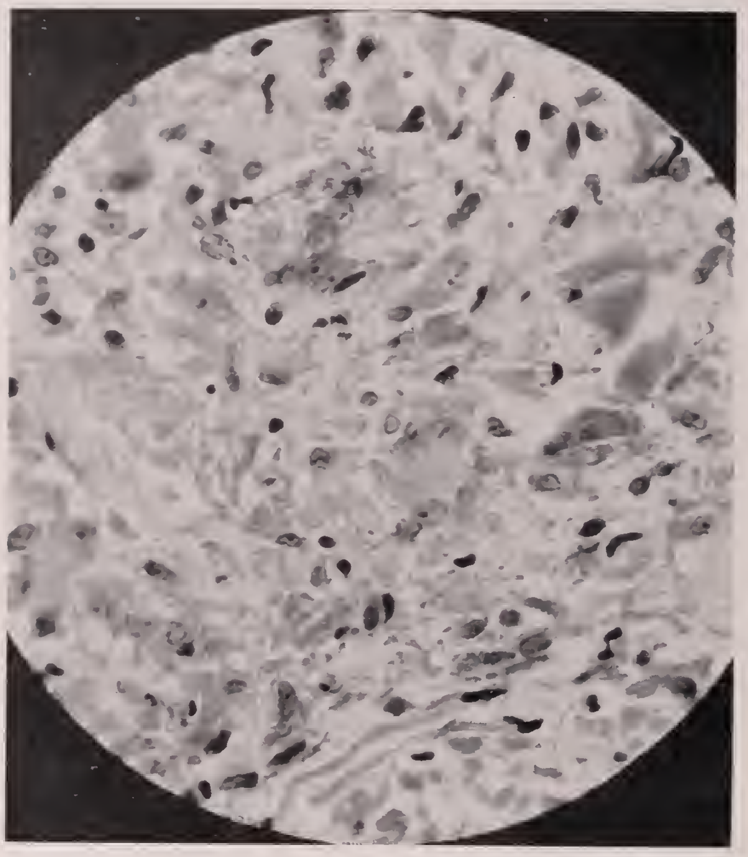

Fig. 1 — Lower biopsy showing granulomatous infiltration (Case 1).

been in 1958 for a similar episode of respiratory infection. At that time, a diagnosis of tuberculosis was entertained but never proved (negative cultures, bronchial and gastric washings, negative inoculation).

Physical examination on admission revealed a well-developed, middle-aged male in mild respiratory distress. His temperature (oral) was 102° F., blood pressure 120/75 mm. Hg and pulse 108/min. Examination of the ears, nose and throat was negative. Examination of the eyes with a slit-lamp was negative. Lacrimal and parotid glands were normal. There were bilateral enlarged cervical nodes. Crepitant rales were heard in the bases of both lungs and a pleural friction rub was audible over the lateral aspect of the left lung. Examination of the heart was negative. The liver edge descended two fingerbreadths below the right costal margin on inspiration. The spleen was palpable two fingerbreadths below the left costal margin. Bilateral moderate enlargement of the inguinal nodes was present. Atrophic scars with a patchy distribution were present below both knees. No subcutaneous nodules were found. A raised indurated hyperpigmented area, 1 cm. in diameter, was present over the right scapula.

Laboratory values: Hemoglobin 11.2 gm.%, white blood count 5,950 with 73% neutrophils, 25% lymphocytes and 2% eosinophils. Erythrocyte sedimentation rate was 64 mm/hr.; LE preparation was negative. Platelets were normal. The urinalysis was negative. The serum calcium was 11.6 mg.%, serum proteins 11.9 gms.% with albumin 3.4 gm.% and globulins 5.5 gm.% Serum electrophoretic pattern showed elevation of the gamma globulin (2.7 gm.%). BSP retention was 16%, cephalin cholesterol flocculation 3+, serum bilirubin 0.2 mg.% at 1 min., total 0.7 mg.% and alkaline phosphatase was normal. The BUN was 20 mg.%. Sputum smears and cultures were negative for acid-fast bacilli and fungi, but revealed Klebsiella sensitive to chloramphenicol. Cultures and rabbit inoculations of material from gastric and bronchial aspirations were negative. Histoplasmin, coccidiodin and Mantoux skin tests were negative. Chest X ray showed a diffuse, fine, nodular infiltrate and linear fibrosis in both lungs; X rays of the hands and feet were negative. Electrocardiograms showed right bundle branch block, nonspecific T-wave changes in leads V4 to V6, and right ventricular hypertrophy. Skin biopsies of the lesions on the lower extremities and on the back revealed noncaseous granulomata, which were also found in biopsies of the bone marrow (Fig. 1), liver, and inguinal nodes (Fig. 2).

The members of this patient's family, who are living in Minnesota, were studied for sarcoidosis. The patient's wife, four children, and a brother were interviewed, given careful physical examinations, chest X rays and Kveim tests. No evidence of sarcoidosis was found. Two sisters were also seen. One had a history of frequent upper respiratory infection, ocular changes, and a cuta-

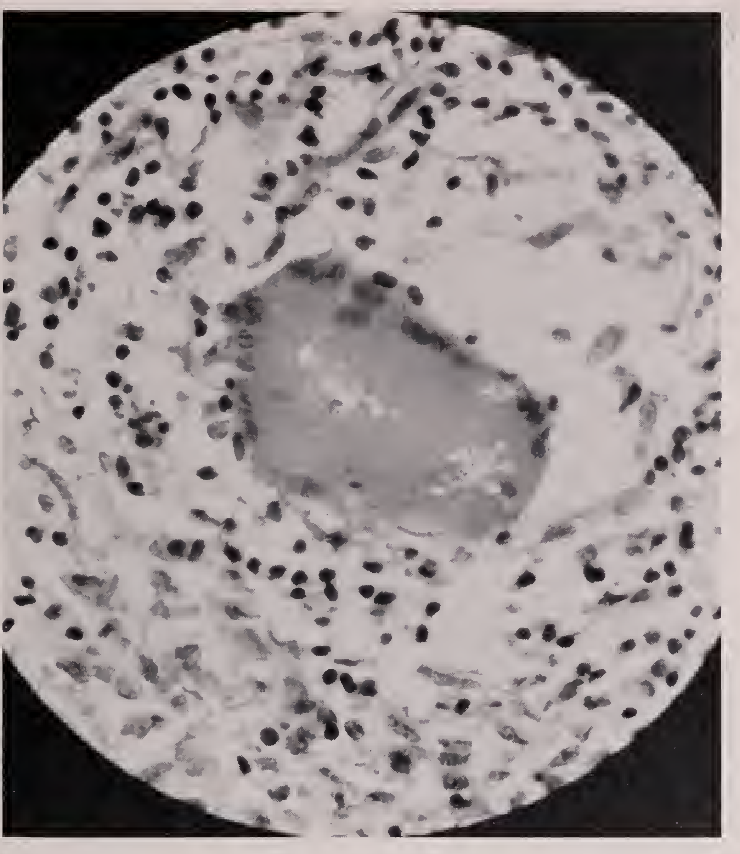

Fig. 2 — Lymph node infiltration (Case 1).

neous lesion on the right forearm suggesting sarcoidosis; but she refused further examination. The other is discussed below.

Case 2

A 37-year-old negro female was first seen in the OutPatient Department of Mount Sinai Hospital in September of 1960. She had no specific complaints and denied a history of cough, fatigability, fever, or weight loss. Three years earlier, she had moved from Alabama where she had spent most of her life. She smoked three cigarettes a day, and chewed pine pitch as a child. In 1956, she was studied at the Public Health Center as a tuberculosis contact and was found to have several subcutaneous nodules on the arms measuring 2.5 to 5.0 cm. in diameter. A chest X ray taken then showed a nodular infiltrate in the apex of the right lung and prominent hilar shadows. A Kveim test was reported as positive. A lipoma had been removed from her right upper arm several years previously.

Physical examination revealed a well-developed, well-nourished negro female in no distress. Examination of the head was negative. There were no abnormal ocular findings. No cervical nodes were palpable. Two subcutaneous nodules were felt in both upper arms. Examination of the abdomen revealed no hepatosplenomegaly. The extremities were negative, except as above.

Laboratory findings: Hemoglobin was 14.5 gm.%, white blood count 5,850 with 78% neutrophils, 18% lymphocytes, 1% monocytes and 3% eosinophils. Urinalysis, Mantoux skin tests, serology, serum calcium and alkaline phosphatase were negative. Erythrocyte sedimentation rate was 32 mm/hr. Chest X ray showed prominent hilar shadows. In October 1960, a second Kviem test was applied on the right forearm and a biopsy of the injection site performed eight weeks later. This revealed noncaseating granulomata (Fig. 3). This patient has been followed with repeated chest X rays, which have failed to reveal recurrence of parenchymal infiltration but continue to show enlarged hilar nodes. She has remained asymptomatic and no treatment has been given.

Discussion

In the light of the possible relationship between pine extracts and sarcoidosis,[7,8] it is interesting to note that both patients lived most of their lives in Alabama, which is in the pine belt of the U.S.A. and that both habitually chewed pine pitch as children. This might also suggest the gastrointestinal tract as the portal of entry, as Palmer[12] suggested when he found that of 60 patients with sarcoidosis, 10% showed tiny granulomata in the gastric mucosa.

There is a significant disproportion between

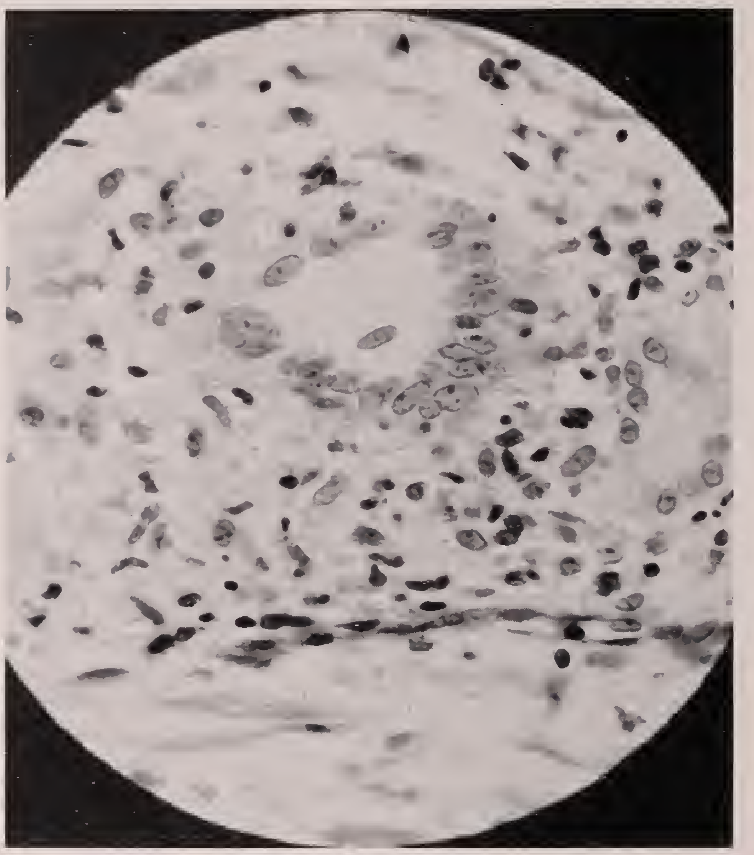

Fig. 3 — Skin biopsy (Case 2) on site of Kveim test.

the occurrence of identical twins among reported cases of familial sarcoidosis and the incidence of identical twins in the general population. This may be partly explained by the fact that the constitution and environment of identical twins are more alike than in nontwin siblings. However, this does not account for the entire discrepancy. We feel that identical twins are much more likely to be investigated together than are nontwin siblings, and that if a careful family search were made in all cases of sarcoidosis, the familial incidence would probably be much greater than is indicated by the small number of recorded cases. In this way new light may be shed on the etiology and pathogenesis of sarcoidosis.

Summary

Sarcoidosis has been described in a negro brother and sister. This represents the 34th report of familial occurrence of this disease. Geographical origin is again emphasized and related to the pine pollen (D.P.A. acid) theory, with the suggestion of an intestinal portal of entry. Careful screening of all family members of the patient with sarcoidosis is suggested.

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WHAT'S YOUR DIAGNOSIS?

A patient, age 66, gave a history of having had "gastric ulcer" for many years. He had taken soda and medicine off and on when his symptoms became more severe. He had observed vague distress in the abdomen from time to time and had been advised by his physician that he had a peptic ulcer despite the fact that the X ray and examination had not revealed a definite ulcer crater.

Within the past year he had lost a considerable amount of weight and found that food distressed him. In the past few months he had observed an increase in the size of his abdomen despite the marked increase in weight loss. His physician did a paracentesis, removing 4,000 cc. of opalescent fluid. Microscopic examination of the fluid revealed a few large plasma type cells but no malignant cells.

At the time of his admission to the hospital he complained principally of weakness and weight loss. He described having bouts of "sweats and chills" which seemed to have no relation to the weather. He thought he has had these sweats and chills off and on for many years, and he considered it as being due to his ulcer.

The physical examination revealed an emaciated man weighing 110 pounds. Examination of the abdomen revealed fluid within the peritoneal cavity. There was an irregular lobular mass palpable in the upper abdomen which seemed to be movable. At times it seemed to be most prominent across the entire abdomen, and at other times was more prominent in the right hypochondrium. This mass was definitely not a portion of the liver as deep palpation could be made between the mass and the costal margin on the right. X ray of the gastrointestinal tract and colon revealed no evidence of pathology but the small bowel pattern was atypical. The jejenum and ilium appeared slightly dilated with an irregular prominence of mucosal fold. No point of obstruction could be made out. Because of this "the pattern was indeterminate and might be related to the ascites, or might be caused by a mesentery vein obstruction."

Routine blood and urine studies were not contributory; bone marrow was likewise not contributory. A preoperative diagnosis of small bowel tumor was made.

What's Your Diagnosis? Turn to page 33.

IT'S THE LAW

Patient Identity Not Permissible

In reporting a case history, or a clinical path conference, the identity of the patient should not be revealed, as the patient may charge invasion of privacy because of breach of confidential communication to the physician. If there is no identification of the patient, there would be no basis for charging that the tort of invasion of privacy had been committed. The name, initial, address, hospital chart number, or identifying date should not be included in a case report lest by these references the patient might be identified. — Stetler & Moretz

An ounce of performance is worth more than a pound of preachment.
—Elbert Hubbard

Hypertension affects many tissues of the body — primarily or secondarily. A world authority provides a refreshing review of this problem.

Pathologic Aspects

of

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JESSE E. EDWARDS, M.D.**
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THE PATHOLOGIST studying patients with systemic hypertension finds lesions which may be divided into three categories.

The first category includes changes related directly to the hypertensive state, which may be primary (idiopathic) or secondary. The second category includes lesions which may be responsible for the tension. The third category includes late complications.

In the first category, the most prominent lesion observed grossly is cardiac enlargement, a change manifested chiefly by hypertrophy of the left ventricle. When cardiac compensation is maintained, the hypertrophy is concentric. When left ventricular failure supervenes, the cavity of the left ventricle dilates as it fails to empty completely with each contraction. In this state, which may be considered a late complication, the thick-walled and dilated left ventricle may show eccentric hypertrophy.

A great deal has been written about the changes in the small arteries and arterioles in systemic hypertension. While these changes may play a role in maintaining a high resistance to systemic blood flow and therefore may be influential in sustaining hypertension, they should be considered secondary to the hypertensive state.

The experience of Castleman and Smithwick[1] indicates that among patients with hypertension on whom biopsy of muscle was done in association with sympathectomy, many failed to show recognizable alterations in the systemic arterioles. Studies of other patients with longstanding primary hypertension showed demonstrable changes in the arterioles of the systemic circulation in each of the organs studied.

These findings support the concept that systemic hypertension has a great influence on the systemic arterioles.

The primary change in the systemic arterioles and small arteries appears to reflect a work hypertrophy of the media of the small arterial vessels in that the medial layer is hypertrophied (Fig. 1, left). Additional changes include various fibrotic lesions of the intima (Fig. 5, lower). In some instances these are nonspecific and densely fibrous, while at other times the intimal fibrous thickening is deposited in a concentric, laminated arrangement and composed of highly

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*Read before the Symposium on Hypertension sponsored by the Methodist Hospital, St. Louis Park, Minn., on September 23, 1961.

**From the Departments of Pathology, Charles T. Miller Hospital, St. Paul and the University of Minnesota, Minneapolis. This study was supported in part by a grant from the National Heart Institute, United States Public Health Service #H5694.

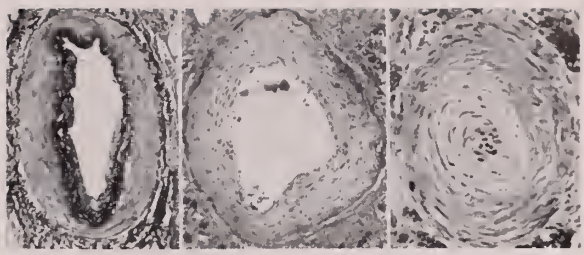

Fig. 1 — Photomicrographs of intrarenal arteries in primary systemic hypertension. *Left* — Medial hypertrophy and elastosis of internal elastic lamina. Elastic tissue stain; X 75. *Center* — Fibrous intimal thickening. H & E; X 150. *Right* — Laminated cellular intimal proliferation. H & E; X 200.

Systemic Hypertension*

cellular connective tissue (Fig. 1, right). The medial thickening, while considered logically as a work hypertrophy, is different from the intimal change, which may be considered as a response to the traumatic influence of the hypertensive state. The traumatic influence may take many forms, including abnormal vibrations of the tense arterioles and turbulent flow within them.

Another change observed in the arterioles or small arteries of the systemic circulation in systemic hypertension is alteration of the intima and the media in which the elements lose their cellular identities and the two layers are converted into a uniform eosinophilic hyalin material. This change sometimes is referred to as fibrinoid change or fibrinoid necrosis. Usually it is not associated with cellular infiltration, a phenomenon that would not suggest an inflammatory process. The vessels converted into the hyalinized process often show significant luminal narrowing. At other times there is obvious necrosis of small arteries and arterioles. This change will be referred to in the consideration of late complications, since it may represent a reaction to hypertensive crises.

The kidney, including all of its elements and small blood vessels, may be entirely normal structurally in the early stages of hypertension. But

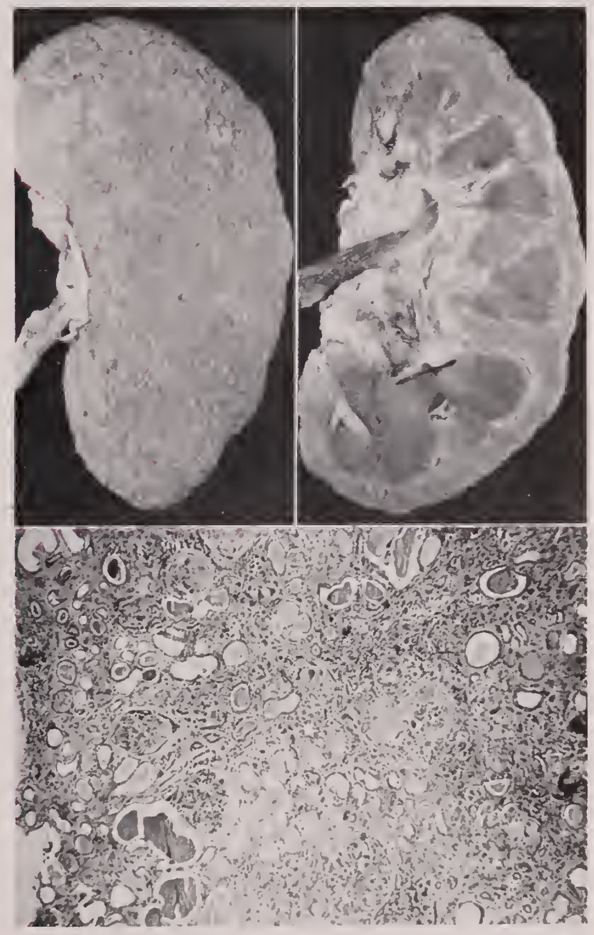

Fig. 2 — Kidney in chronic glomerulonephritis. *Upper left* — External surface. Uniform granularity and reduction in size. *Upper right* — Cut surface. Uniformly thin cortex. *Lower* — Photomicrograph. Scarring of glomeruli, tubular atrophy and interstitial fibrosis. H & E; X 60.

patients who have sustained systemic hypertension of the idiopathic, or primary type, ultimately will have changes in the organ. The kidney with the changes of long-standing hypertension, sometimes is referred to as a vascular kidney, arteriolar sclerotic kidney, or kidney with nephrosclerosis.

Characteristically there is comparatively little reduction in size of the kidney. In some patients it may be normal or even weigh somewhat more than normal. Uniform granularity, characteristic of nephrosclerosis, is associated with cortical lesions which are distributed focally but in a comparatively regular fashion. The focal lesions are centered about vascular occlusive lesions of the type already mentioned. The parenchymal change includes atrophy of tubules and hyalinization of glomeruli. At foci of this change the surface of the kidney shows depression, while between the lesions either the organ is unaffected or its surface is elevated slightly. The latter condition is the result of dilatation of tubules, a process considered compensatory to inadequate renal function. The alternating depressions and elevations, or simply the multifocal depressions, lead to the gross picture of the granular or finely-pitted kidney.

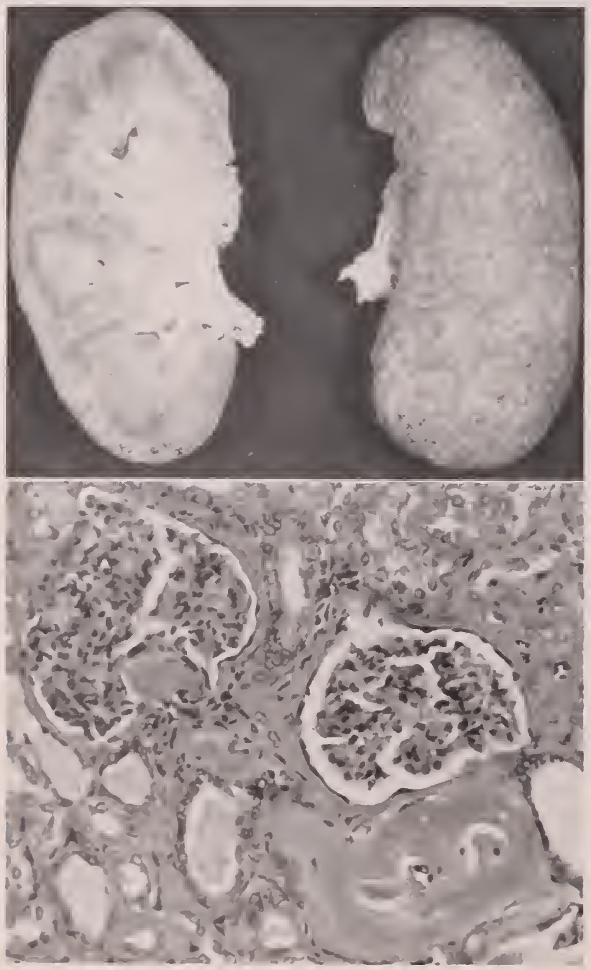

Fig. 3 — Kidney in primary systemic amyloidosis. *Upper* — Cut and external surfaces. Reduction in thickness of cortex reflected in general reduction of size of kidney. *Lower* — Photomicrograph. Amyloid in a renal arteriole and in a glomerulus. H & E; X 200.

In the elderly patient, occlusive lesions in the arterioles may occur which are indistinguishable from the nonspecific fibrous intimal lesions of primary hypertension. Such lesions may be associated with secondary parenchymal loss, such as in hypertension. It may be difficult to tell whether kidneys with lesions resembling those of primary hypertension are consequences of hypertension or simply of the process of aging.

In primary hypertension the kidneys ultimately may show fairly uniform alterations in the form of nephrosclerotic changes secondary to the existence of hypertension.

Renal Lesions Responsible for Hypertension

There are some patients with hypertension in whom there is renal disease that appears to be fundamental in initiating the process of hypertension.

Chronic glomerulonephritis and pyelonephritis are particularly prominent in this sphere.

Chronic Glomerulonephritis

In patients with chronic glomerulonephritis the kidney shows a greater degree of reduction in size than in patients with primary hypertension (Fig. 2.) Among the smallest kidneys are those of patients with chronic protracted glomerulonephritis. The changes in the organ are rather uniform, so that the reduction involves all portions of the renal cortex. The kidney is finely or coarsely granular. If coarsely granular it is the result of foci of tubular dilatations which protrude above the general surface. The dilated tubules, as in primary hypertension, are considered a compensatory mechanism secondary to glomerular failure.

Amyloid Kidney

The kidney with amyloid substance varies considerably in its gross appearance. It is not always a large pale kidney, sometimes considered classic. More often it is reduced in size (Fig. 3). While it usually is more important as a cause of albumin loss and therefore of the nephrotic state, there are isolated instances of hypertension which appear to be the result of this involvement of the kidney.

Diabetic Kidney

The kidney with Kimmelstiel-Wilson syndrome, like the kidney in patients with primary hypertension, may not be materially reduced in size, but often has a somewhat pale, glassy appearance (Fig. 4). Histologically the specific lesion is the nodular thickening of the basal membrane of the glomerulus. Sometimes the fibrous thickening of the glomerular basal membrane may be uniform rather than nodular, representing a less specific picture than the nodular lesion of Kimmelstiel-Wilson syndrome.

The glomerular lesion has been emphasized strongly as the characteristic lesion with the Kimmelstiel-Wilson syndrome. However, it is common that kidneys with such a lesion will show extensive occlusive vascular disease, resulting both from medial hypertrophy and particularly from intimal fibrous thickening (Fig. 4, right). The occlusive arteriolar disease with the Kimmelstiel-Wilson syndrome may play fully as important a role in being a basis for the associated hypertension as do the glomerular lesions.

Polycystic Kidney

The congenital polycystic kidney may be unilateral, but classically it is bilateral, characterized by gross, almost grotesque enlargement of the organs. Each kidney may weigh as much as 1,000 gm. There may be no tissue which, at first glance, grossly resembles renal tissue (Fig. 5, upper). The substance of the kidneys is composed of a collection of cysts of varied sizes, very often up to two inches in diameter.

The problems in polycystic kidney include: (1) basically a small amount of functioning renal tissue, (2) interference by cysts of drainage from the functioning tissue, (3) secondary infection of the functioning tissue incident to obstruction by cysts (Fig. 5, upper), and (4) hemorrhage into cysts which may precipitate acute renal insufficiency.

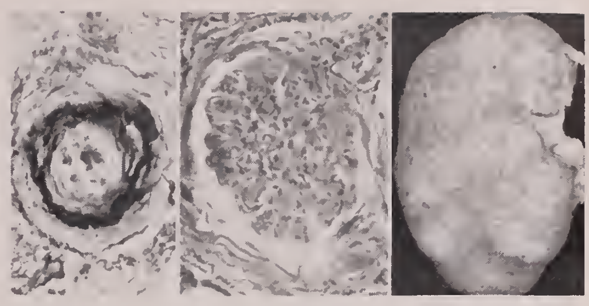

Fig. 4 — Kidney in Kimmelstiel-Wilson disease. *Left* — External surface. In the fresh state the kidney has a transluscent appearance. *Center* — Photomicrograph. Uniform and nodular thickening of glomerular basement membrane. H & E; X 250. *Right* — Photomicrograph. Arterial elastosis and medial hypertrophy. Elastic tissue stain; X 450.

Bilateral congenital cystic disease of the kidney may be associated with cystic disease of the liver (Fig. 5, lower), and there is a tendency for patients with this condition to have congenital aneurysms of the circle of Willis.

The major cause of death in congenital bilateral polycystic kidney is renal failure. Approxi-

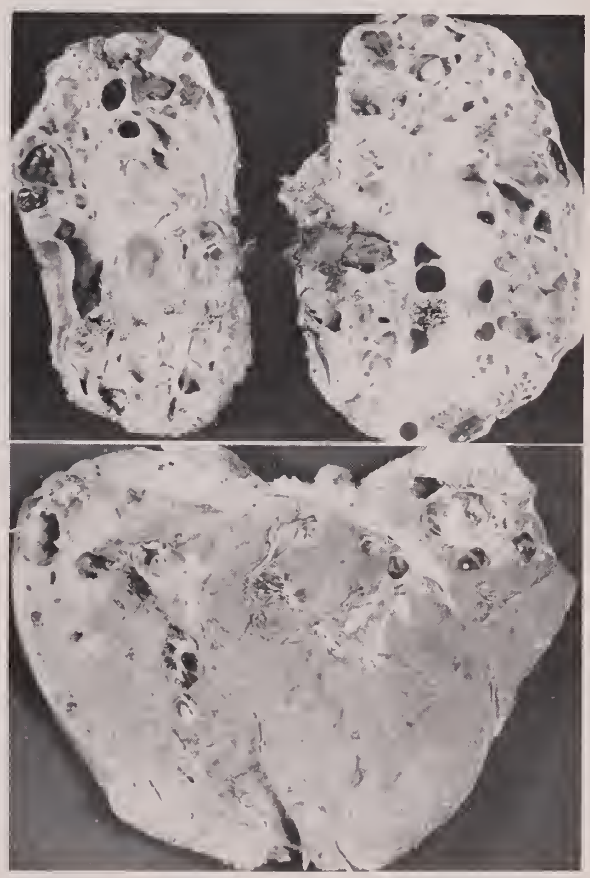

Fig. 5 — Congenital polycystic disease. *Upper* — Characteristic cut surfaces of bilateral congenital polycystic kidneys. Hemorrhages into cysts. *Lower* — Multiple congenital cysts of liver.

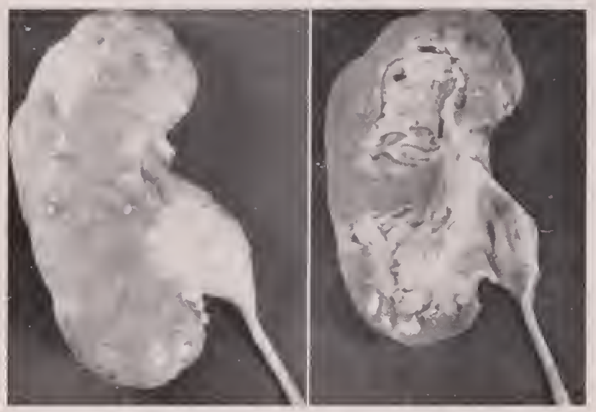

Fig. 6 — Kidney with hydronephrosis and pyelonephritis secondary to stricture at ureteropelvic junction. *Left* — External view. *Right* — Cut surface.

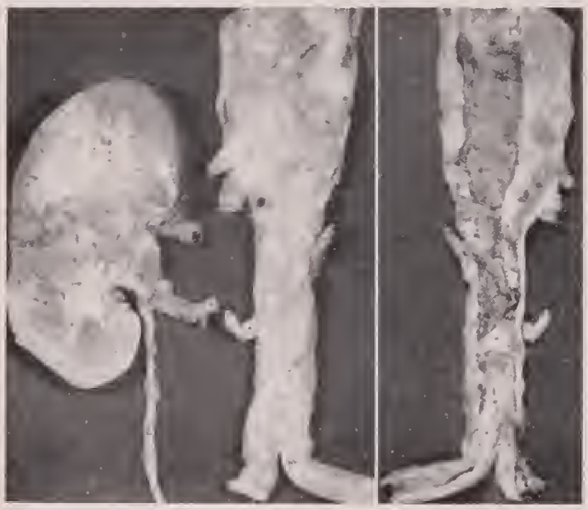

Fig. 7 — Unilateral renal arterial disease. *Left* — Aorta from in front and section of right kidney. The upper of two arteries supplying this kidney is thrombosed and the upper one-half of the kidney is infarcted. *Right* — Interior of aorta from behind. Thrombosis of aorta secondary to atherosclerosis is extensive and caused occlusion of the upper of the two right renal arteries illustrated in *Left*.

mately 10 percent of the patients die from subarachnoid hemorrhage resulting from rupture of the aneurysm of the circle of Willis. In a rare instance congenital bicuspid aortic valve may be associated and may present the problems that pertain in this cardiac anomaly.

Pyelonephritis

The subject of pyelonephritis as it relates to hypertension has as many facets as there are anatomic types of pyelonephritis. The most characteristic picture is that of a bilateral disease with considerable variation in involvement from one area to the other, resulting in gross irregularity of the kidney. Involved areas show broad, flat scars, while those not involved maintain their usual contours. They may even protrude beyond the original surface, as the remaining functional elements undergo compensatory hypertrophy.

Sometimes the pyelonephritis may be a unilateral disease which originates in childhood and shows itself in the adult as a miniature kidney on the involved side and as one larger than normal on the opposite side. In the latter it represents compensatory hypertrophy.

In the healed stage pyelonephritis characteristically is represented by collections of atrophic tubules containing eosinophilic, slightly laminated casts. The aggregate of the involved area may resemble thyroid tissue.

The important part of chronic or healed pyelonephritis as it relates to hypertension probably is dependent upon the vascular lesions which occur in areas of pyelonephritic involvement. These are characterized by intimal fibrous thickening which causes considerable reduction in the lumina of the involved vessels. The basis for the vascular lesions appears to be twofold: (a) the result of a healed arteritis in the areas of antecedent acute inflammation; (b) the relationship with the process of loss of parenchyma with secondary vascular thickening.

This process has been compared by Weiss and Parker[2] with changes occurring in the senile ovary, representing disuse and atrophy of vessels. Whether the term disuse is a proper one in the circumstances is an academic point. However, the luminal narrowing which characterizes it probably is significant.

The interpretation of the importance of the occlusive lesions in pyelonephritis indicates that they are responsible for renal ischemia which, in turn, is responsible for elaboration of pressor substances. While there is a commonly occurring process of vascular narrowing in the areas of pyelonephritis, the areas of the kidney uninvolved by pyelonephritis, including the "uninvolved kidney" in unilateral pyelonephritis, also may show vascular changes. These changes are considered secondary to the hypertension generated by the pyelonephritis. Such lesions involving the portions of the renal substances not involved with the pyelonephritis probably are the important ones from the point of view of maintenance of hypertension after removal of a pyelonephritic kidney.

In patients with pyelonephritis the pathologist may see lesions which appear to be important as underlying causes of the inflammatory disease. When identified, these lesions are usually obstructive in nature. Their importance in setting the stage for pyelonephritis is readily recognized when one appreciates the ease with which pyelonephritis may be induced in an animal in which renal obstruction antecedes delivery of organisms to the kidney. However, the paradoxical situation exists in not a small number of patients with pyelonephritis in whom no lesion of obstruction is identifiable.

When obstructive phenomena are observed, they include obstructive disease in the prostate, neoplasma, stricture of the ureter (Fig. 6), and calculi. The peculiar phenomenon of so-called congenital bilateral hydroureter is an additional condition which may be seen in association with bilateral chronic or healed pyelonephritis. In this condition the ureters are dilated in their entire course, including the ureterovesical junction. The mechanism for the dilation is not apparent and may represent a neurogenic ureteral disease. More work needs to be done to understand the perplexities of this peculiar congenital disease.

Unilateral Renal Atherosclerosis

In some cases of unilateral renal arterial obstruction there may be a peculiar malformation[3] or inflammatory process in the involved renal artery (Fig. 7). Most often unilateral renal arterial disease is derived from atherosclerosis, a process primarily one of aortic sclerosis with renal arterial ostial narrowing. It also may be one in which the atherosclerotic process may reside in the renal artery itself (Fig. 7). In rare instances thrombosis associated with a saccular aneurysm of the renal artery may be a cause of renal arterial narrowing (Fig. 8, upper).

Parenthetically, it should be emphasized that in the patient with hypertension, angiographic studies which fail to reveal filling of a renal artery on one side usually are taken to indicate obstruction of the nonvisualized renal artery. Often, in such conditions, the involved kidney is reduced in size, so that absence of a clearly defined renal shadow in the angiogram is not an important deterrent to the diagnosis of obstructive unilateral renal arterial disease. Confusion may arise in those rare instances where there is congenital absence of one kidney and, concomitantly, of the renal artery to that side (Fig. 8, lower).

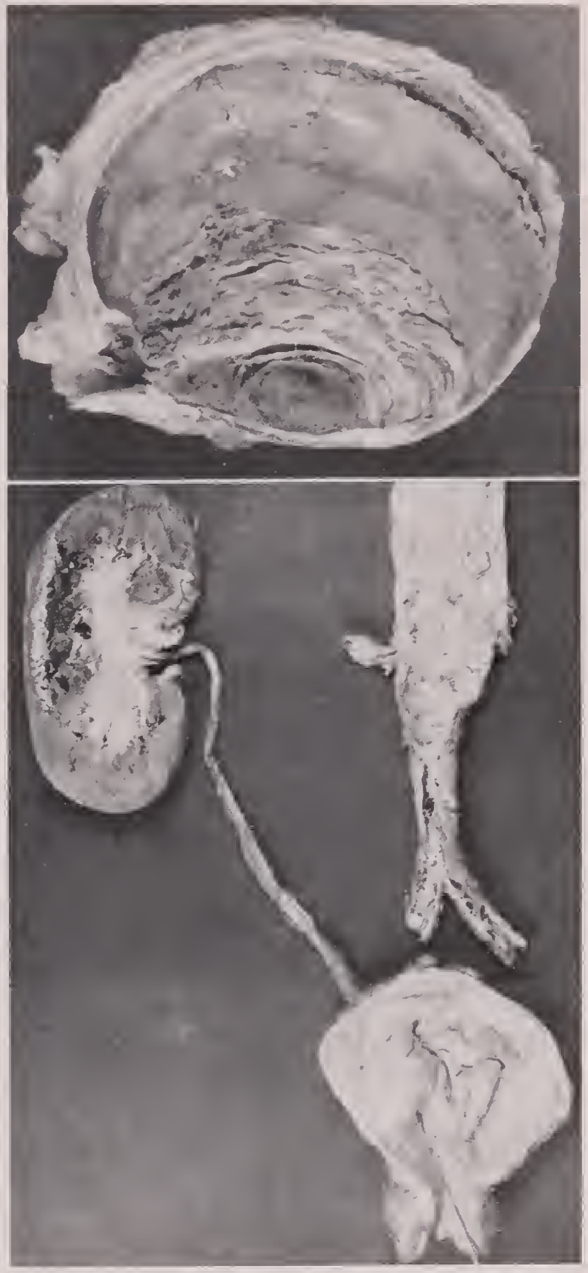

Fig. 8 — *Upper* — Oblique section through a renal artery and a saccular aneurysm thereof. Extensive laminated thrombosis of the aneurysm. *Lower* — Aorta, right kidney, ureter and bladder. Congenital absence of left kidney, renal artery and ureter.

Arteriovenous Fistula

The peculiarities of a renal arteriovenous

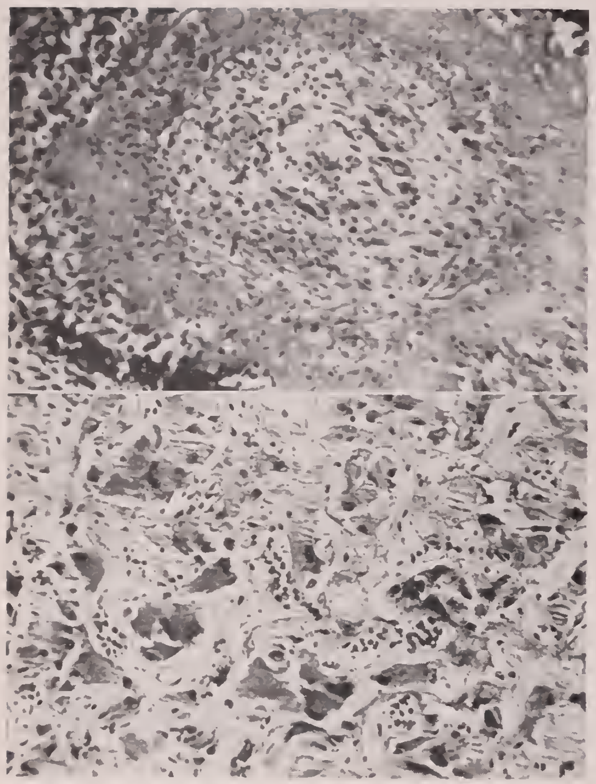

Fig. 9 — *Upper* — Photomicrograph of intrarenal artery in periarteritis nodosa. Necrosis and cellular infiltration of arterial wall. Organizing thrombus in lumen. H & E; X 250. *Lower* — Photomicrograph of pheochromocytoma of adrenal gland. H & E; X 225.

fistula as a basis for hypertension have been emphasized by Scheifley and others[4] as a phenomenon of ischemia of the part beyond an arteriovenous fistula, resulting from the diversion of arterial blood into the vein. In the kidney this has particular significance to hypertension, since the kidney with ischemia may set the stage for hypertension.

Bilateral Vascular Disease

Bilateral vascular renal disease takes one of two forms: narrowing of both renal arterial ostia secondary to severe aortic atherosclerosis, or conditions in which there is obstruction in the intrarenal arterial blood vessels.

The most characteristic disease of this type is periarteritis nodosa, in which the kidney shares fully as much as any other organ in harboring arterial lesions. The gamut of arterial lesions in this disease includes necrosis, aneurysm formation and, most important from the point of view of hypertension, the phenomenon of thrombosis with consequent luminal narrowing or complete obstruction. The multifocal areas of arterial obstruction in this disease are perhaps the basis for renal ischemia and elaboration of pressor substances, the latter being the mechanism through which hypertension complicates periarteritis nodosa (Fig. 9, upper).

While aortic atherosclerosis may be a cause of renal ostial arterial disease, the aortic disease has still another potential as a basis for hypertension. This is represented by the process of embolism of atherosclerotic material.[5] Involvement of intrarenal vessels may be associated with widespread scarring of the kidney, representing areas of infarction or atrophy secondary to arterial insufficiency. It is presumed that the occlusive lesions may be the ultimate cause of elaboration of pressor substance leading to hypertension in this peculiar phenomena.

Extrarenal Lesions Contributing to Hypertension

We have referred to various renal lesions — some unilateral, some bilateral — which appear to be underlying causes of hypertension. There is a series of lesions in extrarenal positions which represent underlying causes of hypertension and have a decided practical importance in diagnosis, since recognition may lead to appropriate therapy and cure.

The Adrenal Cortex

Lesions of the adrenal cortex are recognized as producing two hypertensive syndromes.

The better known is Cushing's disease, which manifests itself in hypertension, a tendency to infection, hirsutism in the female, obesity of the trunk and amenorrhea. Underlying the lesion causing this syndrome may be either bilateral cortical hyperplasia or unilateral cortical adenoma or carcinoma.

The other cortical lesion associated with hypertension is also an adenoma which elaborates aldosterone. Alkalinuria and hypokalemia frequently are found.

The Adrenal Medulla

The tumor of the adrenal medulla which is responsible for hypertension is the well-known pheochromocytoma (Fig. 9, lower). This lesion is usually solid and causes only moderate enlargement of the involved adrenal gland. In rare instances the tumor may be of huge proportions, approximating or exceeding the size of the kidney. In such instances cystic changes with hemorrhage are commonly found in the tumor.

A peculiarity of pheochromocytoma is that it may be responsible for necrosis of myocardial fibers and lead to an electrocardiographic change indistinguishable from myocardial infarction.

Coarctation of Aorta

No discussion of lesions underlying hypertension would be complete without reference to coarctation of the aorta. This condition, previously often unrecognized in the clinical state, is now commonly diagnosed correctly. It has been debated whether the basis for the hypertension represents primarily an obstructive phenomenon caused by the congenital stenosis of the aorta, coupled with inadequate collaterals, or whether it is the result of a nonpulsatile flow of blood to the kidney. That the latter may be the proper explanation is supported by the fact that, although the systolic pressure is lower than normal in the compartment below the coarctation, diastolic hypertension exists in the compartment proximal and also distal to the coarctation.

Late Complications

The hypertrophy of the left ventricular wall and the structural changes which appear in the arterioles of patients with primary systemic hypertension may be considered complications. They appear relatively early in the disease and are in contrast with other complications which in general appear comparatively late in the disease in patients with primary hypertension. We recognize that there are broad limitations to the word "late" as it is used here.

Atherosclerosis

It is well supported that a patient with hypertension has more atherosclerosis than does a comparable patient without hypertension. Important in the sites of the involvement are the coronary arteries, the aorta, and the cerebral arteries. The patient with hypertension is susceptible to various manifestations of atherosclerosis of these major arteries. Admittedly, in the patient with atherosclerosis, it may be impossible to determine whether the hypertension was the important factor in the genesis of the disease, or whether one or many factors contributed materially. As a practical measure, however, the patient with hypertension frequently has associated atherosclerosis with its various ramifications, including myocardial ischemia and infarction and cerebral infarction.

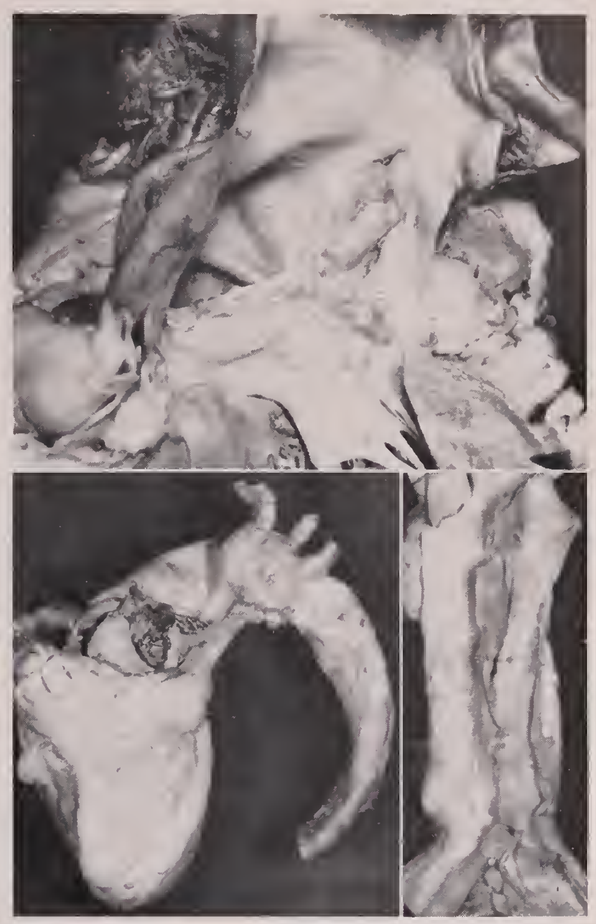

Fig. 10 — Dissecting aneurysm of aorta in a patient with hypertension. *Upper* — Ascending aorta. Internal tear of dissecting aneurysm. *Lower left* — Heart and thoracic aorta. External rupture of ascending aorta which had caused hemopericardium. *Lower right* — Abdominal aorta. Two channels, one true and one false. The latter represents extension of hemorrhage within the aortic wall, a process characteristic of aortic dissecting aneurysm.

Vascular Necrosis

Patients with systemic hypertension may show foci of acute necrosis of small arteries and arterioles, the necrosis often being associated with thrombosis and with infarction of the part beyond. The pancreas and the intestines are among the organs showing such changes. In some instances, episodes of acute abdominal distress in the patient with hypertension may be related to focal infarctive disease. This peculiar complication may result from episodes of sudden elevation of blood pressure. It may be compared with the acute necrosis of arteries occurring in the mesentery after surgical relief of aortic coarctation.

Acute Left Ventricular Failure

Pulmonary edema, sometimes fatal, may develop in patients with systemic hypertension, a complication usually considered the result of acute failure of the left ventricle. It may have yet another mechanism; in the presence of chronic left ventricular failure there is elevation of left ventricular diastolic, of left atrial, of pulmonary venous and of pulmonary capillary pressures.

Pulmonary edema might be prevented if there were adequate pulmonary arteriolar control of the flow of blood into the capillary bed of the lung. If pulmonary arteriolar failure occurred there would be a loss in the restraining mechanism for flow of blood into the lung; and in the presence of greater elevation of the pulmonary capillary pressure (incident primarily to chronic left ventricular failure), pulmonary edema could result.

Chronic congestive cardiac failure, accompanied by chronic passive congestion of the liver and by accumulation of fluid in the subcutaneous tissues and in serous cavities, is recognized as a late complication of hypertension and need not be considered further.

The failing left ventricle, with its complete emptying, may be responsible for thrombosis within the left side of the heart, either in the left ventricle or in the left atrium, particularly the auricular appendage. Such thrombi may serve as sources for embolism involving any portion of the systemic arterial system, including the mesentery, extremities, brain, and even the coronary arteries.

Cerebral Infarction

Cerebral infarction and hemorrhage are among the most feared and the most common complications of systemic hypertension. The extent to which infarction may occur is almost limitless. Episodes of minor degree, either noted clinically or by the absence of a clinical episode, may result from tiny hemorrhages or infarcts in the cerebral substance. Such lesions often are considered complications of localized vasospasm involving the cerebral arterioles.

Gross infarction of a major portion of the brain, such as the internal capsule and basal ganglia, represents a common complication in hypertension. Often no specific vascular lesion is identified as a precipitating cause. Whether hypertension in the absence of occlusive disease may be responsible for such lesions, or whether there is always an anatomic basis for gross infarction is debatable and calls for further elucidation.

Cerebral Hemorrhage

Hemorrhage into the brain of the patient with hypertension may vary from a size that would be noted only under the microscope to gross destruction of an entire cerebral hemisphere. Some lesions undoubtedly are primarily hemorrhagic, while others appear to be infarcts with secondary softening and ultimate complicating hemorrhage.

A special form of cerebral hemorrhage in the patient with hypertension is subarachnoid hemorrhage, which usually results from rupture of an aneurysm of the circle of Willis. Secondary hemorrhage may occur into the cerebral substance. In patients with coarctation of the aorta and in those with polycystic kidneys, this type of hemorrhage is fully as common as that which occurs into the cerebral substance itself.

Dissecting Aneurysm of the Aorta

In the absence of Marfan's syndrome, dissecting aneurysm of the aorta is almost always a complication of hypertension (Fig. 10). The ramifications of this disease need not be elaborated upon in this discussion except to point out that extensive intramural hemorrhage may complicate the internal tear or little dissection of blood may occur. But a localized aortic aneurysm may develop at the site of the internal tear, a site which represents a particularly weak zone, whether or not extensive intramural hemorrhage follows the internal tear.

Uremia represents one of the major causes of death in patients with primary hypertension, particularly those having the higher groups of hypertension — groups 3 and 4. In the patient with hypertension and uremia, a number of lesions develop, related specifically to the uremia rather than to the hypertension. These include pulmonary edema, pericarditis, and focal infarction of the large intestine.

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ANSWER TO WHAT'S YOUR DIAGNOSIS

(From page 23)

At operation a carcinoid of the first portion of the ileum was found producing a partial intestinal obstruction. The proximal loops of jejunum were distended and the walls were hypertrophic to account for the changing palpable mass in the upper abdomen. Inoperable retroperitoneal extension was evident. A resection of the obstructed portion of the ileum and a reanastomosis was done.

Postoperative examination of the urine which had been excreted before the operation revealed serotonin. Had this determination been made preoperatively the exact diagnosis should have been established.

THORSON — BIÖRCK SYNDROME

(Malignant carcinoid syndrome)

Carcinoid tumors are of two varieties: The asymptomatic nonfunctioning, noninvasive type which originates in the appendix (58%) or in the stomach (11%) rarely extend beyond the neighboring lymph nodes and seldom recur after surgical resection.

The invasive tumor which arises in the ileum and may cause widespread metastases to the liver and lung and typical carcinoid endocardial and valvular heart lesions. The symptoms are caused by an excessive production of serotonin from the chromaffin cells of a functioning tumor. These symptoms include peripheral vasomotor phenomena with peculiar flushing in circumscribed skin areas, episodes of cyanosis, respiratory distress from bronchoconstriction, and refractory diarrhea. Serotonin is excreted in the urine and can be measured quantitatively as a diagnostic aid. The normal daily excretion of 5 mg. of serotonin may be increased to 1,680 mg. Hyperserotonemia creates a deficiency of tryptophan, which in turn reduces the formation of niacin and protein.

The invasive type tumor arising in the ileum may cause cardiac lesions consisting of endocardial fibrosis, nonrheumatic pulmonary stenosis, and tricuspid insufficiency. Cardiac failure may eventually develop.

Autopsies have revealed gastric or duodenal ulcers in 38% of one series.

Surgical removal of the tumor may provide a long term clinical arrest but does not eliminate an eventual fatal result. No effective therapy of the malignant metastatic syndrome has been evolved. — Durham (See page 23)

They did not forgive him for having succeeded. — Hugh McLeaue "The Rish Tobers"

A mighty name has all the power of a fairy's wand. — Balzac

Photographic Contest

The Editors of Minnesota Medicine, in collaboration with the Doctors' Photographic Society of Minneapolis, take pleasure in announcing a monthly photographic contest. The contest is to promote an interest in photography in the medical profession. First prize each month will be publication in full color of the winning picture in Minnesota Medicine.

The following rules will govern the conduct of the contest:

1. Only doctors of medicine are eligible to submit pictures, and the picture must have been taken or composed by a physician.
2. Each contestant may submit not more than two pictures each month.
3. Only color transparencies, 35 mm. to 2¼" can be considered.
4. Each slide should be labeled with the maker's name, address, and the identifying title.
5. Slides should not be mounted in glass, but can be protected in plastic sleeves or envelopes.
6. Each entry must be accompanied by a self-addressed, stamped envelope if return of the picture is desired. Returns will be made shortly after the close of the contest each month. The winning photograph will be retained but will be returned after it has been used.
7. The deadline date for entry will be the 10th of each month and the winner of each month's contest will be announced in Minnesota Medicine in the subsequent issue. The date of publication will be three to six months in advance.
8. There will be no limitation on subject material except as indicated in item 10.
9. Model releases will be requested of winners where appropriate.
10. Judges will be selected by the editors of Minnesota Medicine and the Doctors' Photographic Society. The judges will be guided by the precepts of the Photographic Society of America, and winners will be based on appropriateness, interest, impact, and technical excellence.
11. The editors of Minnesota Medicine and the Doctors' Photographic Society cannot be responsible for entries lost or damaged, but every effort will be made to protect submitted pictures.
12. The first judging will be made in the month of February and monthly thereafter.

Your pictures are hereby invited. Please submit pictures to:

Photo Contest Editor
Minnesota Medicine

Gastric Freezing in the Treatment of Peptic Ulcer

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GASTRIC FREEZING has recently been developed as an elective and definitive procedure in the treatment of several manifestations of the peptic ulcer diathesis. It follows an earlier experience (1958) with more moderate degrees of gastric hypothermia for the control of massive upper gastrointestinal tract hemorrhage.[1,2] The newer technique, gastric freezing, is not intended to supplant gastric cooling for hemorrhage, but represents an effort to impair the secretory apparatus of the gastric mucosa for a sufficient period to permit symptomatic relief of ulcer pain and healing of ulcer craters.

Extensive animal experimentation has demonstrated the ability of one or more episodes of gastric freezing to depress significantly, and in some instances suppress completely, acid secretion in isolated canine pouches for periods as long as 18 months.[3-9] Secretory depression in the intact stomach of both dog and man attending gastric freezing is far less consistent and striking and considerably shorter in duration. However, in the intact stomach of the dog, previous gastric freezing significantly reduces the incidence of peptic ulceration following such ulcer provoking procedures as the implantation of histamine in beeswax, or transplantation of the gastric antrum to the transverse colon. In the rat, prior gastric freezing significantly reduces the development of ulcers associated with the combined stress of

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Supported by Grants from the U.S.P.H.S. and the Donald J. Cowling Fund.

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starvation and cold. The protracted achlorhydria attending freezing of isolated canine gastric pouches warrants the suggestion that improved techniques of clinical gastric freezing will be attended by longer periods of gastric secretory depression.

Indications and Contraindications

The first patients subjected to gastric freezing were those referred to the Surgical Services of the University of Minnesota Hospitals for elective surgery for duodenal ulcer disease. However, the stomachs of 150 dogs had been frozen before our first patient was submitted to gastric freezing. Our indications continue to be limited to patients with intractable ulcer. The majority of patients treated by us to date have had chronic duodenal ulcer, with failure of response to good medical management, previous episodes of hemorrhage, or prior perforation with recurrent symptoms. Early experience indicated that any degree of gastric retention of pyloric obstruction is a contraindication to gastric freezing, because gastric mucosal edema attending freezing usually augments pre-existing obstruction. Moreover, gastric ulcer has been observed to follow gastric freezing in patients having pyloric obstruction. Other indications for gastric freezing include postgastrectomy stomal ulceration, stenosing peptic esophagitis, with or without hiatus hernia, and benign gastric ulcer. The latter group has been treated essentially in the healed phase, in an effort to prevent recurrence. Our limited experience in freezing the stomachs of a few patients with active gastric ulcer craters, in whom we could be reasonably certain that cancer could be satisfactorily excluded, has not been very reassuring.

Technique

A few modifications of the original technique have evolved during the course of the past 18 months. However, the basic principles remain the same. Following local anesthesia of the throat, a deflated gastric balloon attached to a double lumen tube, is inserted. The balloon is gradually distended with sufficient alcohol to cause a feeling of local distension, without pain. This volume currently averages 1100 cc. in the adult. Perfusion of the balloon with 80% cold alcohol from a hypothermia machine* is then begun. Less concentrated alcohol markedly reduces the flow rate of the hypothermia machine, due to marked increases in viscosity at −17° C. Extreme care must be utilized in limiting the inflow temperatures of the perfusate to −17° C. and the outflow temperatures to −10° C. Our current perfusion time is 50 minutes. In addition, caution is essential to prevent overdistension of the gastric balloon, or systemic hypothermia. External body warming by electric blankets is useful in preventing systemic temperature drifts greater than 2° C.

Following the perfusion, a 15-minute thawing period is observed with the balloon distended and in place, but without perfusion. The alcohol is then gradually withdrawn and the balloon gently removed. The patient is permitted to eat within two hours and is generally discharged from the hospital the following day.

Following freezing, the patient is generally instructed to remain on a bland, soft diet for approximately 10 days, during the period of gastric mucosal edema. He then gradually advances to an unrestricted diet, avoiding alcohol and caffeine. Ulcer medication is also dispensed with following freezing. Follow-up X ray and gastric secretory observations are performed in our study group at one day, six weeks, three months, six months, nine months and 12 months after freezing.

Results in Duodenal Ulcer

More than 80 per cent of our 365 patients to date have had chronic duodenal ulcer, with intractability as the primary indication for freezing. In fact, most of our patients have been candidates for surgery. In the duodenal ulcer group, approximately 90 per cent obtain immediate symptomatic relief, and in 71 per cent marked immediate secretory depression has been observed.

Secretory Depression

Secretory depression, which includes a 58 per cent incidence of achlorhydria the night following freezing, does not persist indefinitely. At six weeks following freezing, 41 per cent of the patients continue to have significant degrees of secretory depression (greater than 50 per cent depression, based on milli-equivalents of free acid in an eight hour unstimulated overnight aspiration). By three months only 33 per cent exhibit significant depression and at six months this number is reduced to 11 per cent. However, this profound though transient secretory depression is prolonged enough to permit healing of ulcer craters and continued symptomatic relief.

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*Swenko Research and Development Co., Minneapolis

Forty-five per cent of the patients treated and followed for six months or more continue to be completely asymptomatic without dietary restriction or medication. An additional 19 per cent have had some recurrence of symptoms, which has been controlled by refreezing. The remainder have either continued to have ulcer symptoms and are unwilling to undergo additional episodes of freezing or have been operated upon. Twenty of the 286 duodenal ulcer patients have been subjected to surgery, generally for the late development of gastric retention and pyloric obstruction, or for hemorrhage. At least six, and perhaps eight, of these 20 patients, either would not be candidates for freezing under our present criteria because of pre-existing pyloric obstruction, or were operated upon without adequate indication for surgery.

An active ulcer crater has been demonstrated in only 15 per cent of the duodenal ulcer patients; the remainder have had chronic duodenal deformities demonstrable by conventional X ray techniques. In all but two of the patients with demonstrable active ulcer craters there was evidence of healing within six weeks after a single freeze. These two required subsequent episodes of refreezing before evidence of healing was apparent.

Results in Stomal Ulcer

Thirty-eight patients with postgastrectomy stomal and marginal ulcer have been treated to date.[10] Of these, 10, who failed to receive persistent symptomatic relief after a single freeze, have since been subjected to refreezing. In these patients, fluoroscopic placement of the gastric balloon was not practiced at the time of their initial freeze. Nine of these ten have been converted to good or excellent results following such refreezing. However, one patient continued to have ulcer pain and a persistent jejunal crater. He also represents the only complication seen in this group — a small gastric perforation with a dissection tract, which healed on a conservative medical regimen. However, the stomal ulcer did not heal and the patient was subsequently subjected to surgery — the only patient in the stomal ulcer group requiring surgery for peptic ulcer disease. Included in this group is one patient with a proven Zollinger-Ellison syndrome, including multiple hepatic metastases, whose severe ulcer diathesis has been controlled completely over an eight-month period by two gastric freezes.

Five patients with stenosing esophagitis treated thus far by gastric freezing have had very encouraging results, with marked reduction in the frequency with which dilatation is required, as well as symptomatic relief from esophagitis.

Complications

While there has been no mortality either directly or indirectly attributable to the gastric freezing procedure in our experience to date, two significant complications have been observed.

Melena

Gross melena has been observed in 12 patients, and has invariably responded to conservative medical management when this has been invoked. However, two of our early patients returned to distant cities where their surgeons advised gastric resection. It is our feeling that this complication represents a mild hemorrhagic gastritis following freezing and that it is a transient and self-limiting problem.

Gastric Ulcer

The second complication, the development of gastric ulcer in patients treated for duodenal ulcer, is considerably more distressing.

Nine of our 365 gastric freeze patients developed gastric ulcers following freezing, and in two, free perforation occurred, requiring laparotomy and closure. A postfreeze gastric ulcer is undoubtedly due in part to the jet-thrust effect of the very high flow rate of cold alcohol ejected against a fixed area of the greater curvature. Multiple lateral openings on the inflow tube, providing for consideration diffusion of the inflowing alcohol has markedly reduced the incidence of this complication. Moreover, development of additional technical refinements, including a device which will permit the inflow tube to remain in the center of the intragastric balloon, affords promise that this complication may be completely eliminated.

Attention to a large number of technical considerations is of paramount importance in gastric freezing. Such items as the concentration of the alcohol and its temperature, the accuracy of the temperature gauges on the hypothermia machine, balloon wall thickness and distension, maintenance of systemic normothermia, and the duration of the perfusion are extremely critical. Deviation from the carefully delineated safe range in any of these areas may be fraught with hazard. However, when the details of technique are carefully observed, the procedure has proven to be free of mortality and subject to low and acceptable rates of morbidity. More critical evaluation and appraisal of some of these technical factors, we believe, will ultimately or virtually eliminate the factor of morbidity.

Discussion

Gastric freezing as a definitive treatment for the peptic ulcer diathesis is presently under evaluation in a number of university and hospital centers throughout the country. Our current experience includes 365 patients, treated with 461 separate episodes of freezing, over an 18-month period. The patients have been carefully selected in an effort to document the severe degree of their ulcer disease to test the method adequately. In addition, the standard items of medical dietary control and drug therapy have been discontinued following freezing, to challenge further the peptic ulcer potential in these patients. To date, the results appear to be quite encouraging.

We still look upon gastric freezing as an experimental venture. It is our feeling that for the present, gastric freezing should remain limited to those university and hospital centers willing and able to select, test and follow their patients, in order to obtain independent and objective evaluations of the effectiveness of gastric freezing in controlling various manifestations of the peptic ulcer diathesis. Such limited clinical trials should probably continue until independent surveys of adequate numbers of patients have been made and reported in the medical literature, and the place of the procedure has become more carefully defined.

Hospital teams desiring to undertake gastric freezing should insist that all personnel in the team acquire first-hand experience with the technique in an experimental laboratory, observing the effects of freezing and the many important details of operation of the hypothermia machine, before embarking upon clinical trials. Purposeful deviation from the lessons learned in the laboratory, and the clearly defined safe limits of the procedure, will only serve to emphasize the hazards and dangers of ignoring these guidelines in the course of clinical application.

Evidence of the safety of the procedure in careful hands includes experience with an additional 243 patients in five co-operating hospitals in the Twin Cities area, and an additional 233 patients treated at five co-operating university centers throughout the country. These cases, when added to our own, total 841 cases treated without mortality.

Summary and Conclusions

Gastric freezing appears to be a safe, simple, and useful tool in the management of several aspects of the ulcer diathesis and appears worthy of further objective evaluation in the hands of teams at university centers and hospitals, where a group is willing to undertake the responsibility.

Three hundred and sixty-five patients have been treated with 461 episodes of freezing without mortality. Twelve instances of melena and nine of postfreeze gastric ulcer have been observed. Forty-five per cent of the patients followed for six months or longer continue to have complete symptomatic relief following a single freeze and an additional 19 per cent have been maintained symptom-free by one or more episodes of refreezing. Additional large scale objective clinical trials and long-term follow-up studies will be required before the procedure can be considered acceptable for general adoption by the profession.

The importance of the technical factors in the safety of gastric freezing can not be overrated. These include:

1. Per cent of alcohol in perfusate
2. Depression of inflow and outflow temperatures during perfusion.
3. Maintenance of normothermic systemic temperature.
4. Duration of perfusion.
5. Thickness of balloon wall.
6. Distension of balloon.
7. Keeping the end of the perfusion tube centered within the gastric balloon.

In the hands of interested, experienced, and careful observers, the procedure appears to be free of mortality, and the results to date suggest that gastric freezing may come to play an important role in the management of several aspects of the peptic ulcer diathesis.

Addendum

Since this paper was presented May 20, 1963, our series of clinical gastric freezing has grown to 543 patients, attended by no mortality. Over the past six months, the incidence of post-freeze melena has remained approximately the same. However, post-freeze gastric ulcer has been observed less frequently; no such complication having been observed in the 104 patients subjected to gastric freezes since July 1, 1963.

Uniform freezing of the gastric wall, it is to be acknowledged, is rarely achieved. In a number of instances, a small lead-balloon anchored in the duodenum has been used to insure more consistently achieving depression of the antral gastric temperature during perfusion. The size of the gastric freeze balloon has been increased to hold up to 1400 ml. of the alcohol solution. Current practice suggests 1100 ml. is the average filling volume of the balloon during perfusion. The rate of perfusion has been increased up to 4,000 ml. per minute. Use of I. V. low molecular weight dextran (Pharmacia 2 gms. per kilo) to minimize sludging of blood in the vessels of the frozen stomach, though not lessening gastric secretory depression, has permitted return to an hour's freeze at temperature inflows of −20° to −22°C. Outflow temperature depressions of −12°C. are quite regularly achieved within 15 minutes of commencement of the perfusion. During the last 10 to 15 minutes of the hour's perfusion, the desired −22°C. inflow is usually achieved, without augmenting the incidence of post-freeze complications. Whereas erosions or superficial ulcers have not been eliminated with employment of low-molecular weight dextran, the extent and depth of such lesions have been strikingly attenuated. Recent observations in the experimental laboratory lend credence to the belief that clinical gastric freezing by open, rather than balloon perfusion, may not be far off. An increased opportunity will thus be provided for more intimate contact between the cold perfusant and the parietal and chief cells in the gastric tubules.

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7-11 will appear in reprints or can be obtained from the author.

Many a live wire would be a dead one except for his connections. — Wilson Mizner

Pyelonephritis

PYELONEPHRITIS IS present in approximately 15 per cent of all patients coming to necropsy, playing a significant role in the illness of at least one-third of these patients.[1,2] Hence, one may justifiably assert that pyelonephritis is today the most common disease with greatest immediate potential for treatment among the chronically and seriously ill. The term "potential for treatment" is used because pyelonephritis is an infectious disease, the causative agent of which can be isolated from the patient and studied in the laboratory, and specific therapeutic agents are available which exert an inhibitory effect against the microorganisms producing the infection.

The classic case of acute pyelonephritis, characterized by the sudden onset of fever, flank pain, and dysuria, and producing pyuria and bacteriuria, is not difficult to recognize. It is usually due to antibiotic-sensitive strains of coliform bacilli; and the suppression of the infectious process by the administration of one of many antimicrobial agents is no great problem.

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An authority on renal disease points the way to better control of urinary tract infections.

Approaches to the Treatment

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Recognition and Diagnosis

Chronic or recurrent infections of the urinary tract, however, present many problems in recognition and management. The solution to some of these problems requires a reorientation of thinking, which includes the concept that urinary infections, like respiratory infections, represent a group of disorders rather than a single disease, with a natural history and response to therapy differing from, and depending on, the characteristics of the causative organism, the anatomic site of the infection, and the route of inoculation. While infections in one part of the urinary tract may predispose to infections in another, some patients may have evidence of cystitis or urethritis for years without developing infection of the kidney parenchyma. Others may have a rapid ascension of the infectious process. Even in infections at one site, such as the kidney tubules, the course of the disease and its management may be quite different if it is due to a gram-positive coccus as compared to a gram-negative bacillus.

Early Recognition

One of the greatest problems associated with the treatment of pyelonephritis is its recognition, and particularly its recognition prior to development of irreversible structural and functional changes. With the most precise means available today it is not always possible to define anatomically the extent of the inflammatory process. It is often difficult to differentiate contaminating microorganisms from those playing a significant role in the infectious process. The use of the quantitative cultural technique has greatly improved the reliability of urine cultures as a means of establishing the causative organism. Exceptions exist, however, in the accepted criteria of bacterial counts of 10,000 organisms per milliliter of urine or greater, being indicative of significant bacteriuria. The number of organisms may be diminished under the influence of suppressive but not curative therapy, or when the disease is in a less active phase. There is evidence also that some organisms, notably the gram-positive cocci, may produce progressive pyelonephritis, though a relatively small number of organisms are excreted in the urine.[3]

Pyelonephritis is often associated with marked discrepancies between the clinical signs and symptoms of the disease and the severity of the process. There is often an inverse relationship between the symptoms of urinary tract irritation and the seriousness of the infection. The patient is most aware of something being wrong with his urinary tract when he has the relatively insignificant urethritis, while with severe and diffuse infections of the kidney parenchyma he may have no symptoms specifically referable to the urinary tract. Progressive chronic pyelonephritis, ultimately leading to renal failure, may often be manifest as asymptomatic bacteriuria. Many patients with active pyelonephritis will have no increase in the number of pus cells in their urine when isolated specimens are examined. Consequently, the patient and the patient's urine must be repeatedly and carefully studied, utilizing quantitative methods, if the varying manifestations of pyelonephritis are to be properly interpreted.

Therapy

In spite of an intensive study of pyelonephritis in several medical centers in this country and abroad, not a great deal is known about the relative value of the various approaches to treatment. This is true partly because of differences in interpretation of the criteria for diagnosis of pyelonephritis, but also because of the difficulty in determining the long-term effect of a particular treatment regimen. It is quite likely that the disease is self-limiting in some patients, so that cure will occur with any form of treatment.[4,5] It is also quite likely that some instances of "chronic infection" represent repeated new infections rather than relapses of an old infection. The manifestation of renal disease resulting from the changes in renal histology and physiology must be separated from those of the infectious process itself. If the injury produced by the infection is great enough, removing the infectious agent will not necessarily allow the reversal of the effects of the process. The urine, then, may be transiently sterilized in almost every patient with a urinary tract infection; but in some instances relapses or reinfections occur, or there may be irreversible functional damage, so that long-term and careful follow-up of treated and untreated patients is required to evaluate the merits of various treatment schedules.

Eradication of Causative Organism

One is left then with the selection of a rational approach to the treatment of urinary tract infections, based on what might be expected to be beneficial from what is known of the pathogenesis of the process and the empiric experience of the physician treating the patient. The objective of the approach should be to aid in the healing of the inflammatory process and the restoration of normal renal function. This involves the eradication of the causative organism in the kidney tissue and in the urine. In patients with severe infection, long-standing or recurrent infection, the infectious agent should be suppressed and reinfections prevented until the inflammatory reaction, which may increase susceptibility to reinfection by interfering with the free flow of urine, has subsided.

There are differences of opinion as to how these objectives may be achieved. Most investigators agree that acute infections of the lower urinary tract with low bacterial counts require little attention, since they either subside spontaneously or respond promptly to almost any urinary antiseptic.[1,4,5,6] If this type of infection occurs during pregnancy, however, it should be considered more seriously; and suppressive therapy, usually in the form of sulfonamides, should be continued throughout pregnancy.[4] In every patient with "cystitis" several follow-up quantitative urine cultures should be carried out in order to be sure that the infection has properly subsided and that it has not been part of a more extensive process.

There is also general agreement that patients with an isolated episode of acute pyelonephritis can usually be treated effectively with any antibacterial agent active against the specific causative organism as determined by in vitro sensitivity tests. Continuation of therapy for a week or two is usually adequate.

Chronic and Recurrent Problems

When one approaches the problem of the treatment of chronic or recurrent infections many problems arise and considerable difference of opinion exists as to the details of the program on management. It is the patient with this type of infection, however, that everyone agrees should have a thorough diagnostic study, including intravenous and, if indicated, retrograde pyelograms, and all possibilities for interference with free flow of urine should be investigated and corrected.

Antibacterial Therapy

While baseline kidney function tests are being completed, antibacterial therapy should be instituted. Agents active bactericidally against the individual infecting organism should be used in optimum doses for a week after urine cultures are negative and the clinical symptoms and signs of infection have subsided. Since the agents which are predominantly bactericidal in their effect (penicillin, streptomycin, kanamycin, neomycin, polymyxin, colistin, and bacitracin) also require parenteral administration, hospitalization for therapy is almost always necessary. If an orally-administered antimicrobial agent is active against the causative organism, it should be begun during the course of therapy with the bactericidal agent and continued for a period of time deemed adequate for the inflammatory process to heal. Repeated quantitative cultures should be carried out during this period so that significant shifts in flora can be recognized and the antibacterial therapy adjusted accordingly. In some instances this type of suppressive therapy must be continued for periods up to six months.

It is appropriate to reiterate that not all students of pyelonephritis agree with this chemotherapeutic approach.[7] Many feel that as much can be accomplished by one or two weeks of therapy as by prolonged therapy, and others feel that there is no advantage of bactericidal agents over bacteriostatic drugs, or even urinary antiseptics. Time and additional experience will help make these decisions.

Antibacterial therapy may not always be adequate to control the inflammatory process, and surgical procedures must be resorted to. In the chronic urinary tract infection of young girls, for example, there is considerable building up of granulation tissue at the bladder neck, interfering with complete emptying of the bladder and consequently with control of the infection. Sometimes surgical resection of this tissue will allow better vesical drainage and thereby insure better control of the infection. If on the other hand, the resection is not followed by effective antimicrobial therapy, the granulation tissue is likely to reappear. It may be that an obstruction, microscopic in size, and occurring within the tubules, explains the tendency of pyelonephritis to relapse and become chronic. Certainly the histologic picture of chronic pyelonephritis with dilated tubules suggests strongly that this occurs. Under such circumstances possible advantage might exist in concomitant use of antibacterial agents and anti-inflammatory compounds. No information is available on this subject.

Permanence of Therapy

What are the chances that the treatment of pyelonephritis will produce permanent cure? If the causative organism is susceptible in vitro to the antimicrobial agent being administered, transient sterilization of the urine can be attained in almost all patients;[7] but the permanence of the sterilization seems to depend mostly upon the presence or absence of urologic abnormalities interfering with free flow of urine.[1] The frequency with which uncomplicated acute pyelonephritis is effectively treated is not known, but evidence from serial renal biopsies indicates that at least some patients are cured.

Summary

Difficulty in determining true effectiveness of various methods of treating infections of the urinary tract has prevented establishment of precise regimens of treatment which can be considered superior to others. Consequently, judgment regarding therapy must be based on what appears rational as derived from knowledge of the disease and empiricism.

The treatment of "cystitis" or urinary tract infection associated with low bacterial counts may be purely symptomatic or may involve the use of any urinary antiseptic. If this therapy is not effective, more thorough diagnostic procedures should be carried out and more intensive therapy instituted. Such infections, when they occur during pregnancy, should be treated throughout pregnancy with suppressive drugs (such as the sulfonamides).

Treatment of an isolated episode of acute pyelonephritis attended by high urinary bacterial counts can usually be accomplished with any antibacterial agent active in vitro against the specific causative organism. Therapy should be maintained one or two weeks.

Patients with chronic or recurrent urinary tract infections are least likely to be permanently cured. Consequently, every effort should be made to correct any anatomic or functional defects interfering with the free flow of urine. Intensive specific antibacterial therapy (preferable a bactericidal agent) should be administered for five to ten days, and suppressive therapy with an agent active against the causative organism should be continued until all evidence of inflammation has subsided and there is unobstructed flow of urine.

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Patron Saint of January

Of all the January saints Simeon Stylites is the most unconventional and arresting figure, to whose miraculous powers were ascribed many bodily and spiritual healings. In fact he was so persistently and ardently importuned for cures by the multitudes that in self-defense he retired to the top of a pillar, a move which reduced his availability but failed to diminish his popularity.

He was "the best known of the pillar saints, the son of a Cicilian shepherd, who became a monk in a Syrian monastery while still a boy; later he was dismissed from another monastery for his imprudent austerities. After some years as a hermit people used to throng to him, and it was to avoid them that he first took up his residence on a platform at the top of a pillar. He thus lived for thirty-seven years, gradually increasing the height of the pillar from about ten feet to about sixty, and for some forty years he refrained entirely from food throughout Lent: sometimes he was so weak that he had to tie himself to a pole lest he fall off his pillar. This extraordinary way of life aroused admiration (and imitation) as well as curiosity, and emperors and patriarchs as well as simple folk came to consult him. St. Simeon died on his pillar in his sixty-ninth year in 459."

What an unbelievable but unforgettable picture! Emperors, patriarchs, and simple folk standing at the base of a pillar with the fanatical but saintly Simeon perched atop it, dispensing cures and advice!

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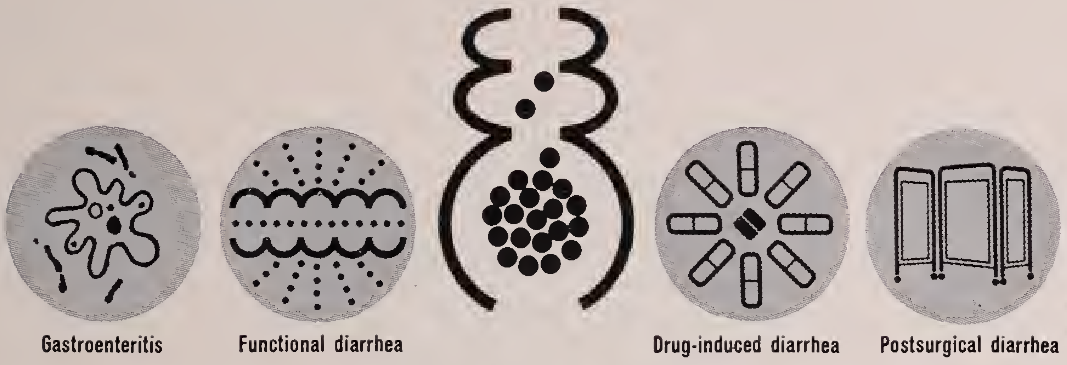

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The relatively few conditions in which Lomotil has given less than satisfactory control have been, for the most part, those such as severe ulcerative colitis in which too little anatomic or functional capacity of the intestines remains for the motility-lowering action of Lomotil to have effect.

It should be noted, however, that Lomotil has proved highly useful in mild to moderate ulcerative colitis and in several other refractory forms of diarrhea.

The recommended initial adult dosage is two tablets (2.5 mg. each) three or four times daily, reduced to meet the requirements of each patient as soon as the diarrhea is controlled. Maintenance dosage may be as low as two tablets daily. *Children's* daily dosage (in divided doses) varies from 3 mg. for a child of 3 to 6 months to 10 mg. for one 8 to 12 years of age. Lomotil is an exempt narcotic; its abuse liability is low and comparable to that of codeine. Recommended dosages should not be exceeded. Side effects are relatively uncommon but among those reported are gastrointestinal irritation, sedation, dizziness, cutaneous manifestations, restlessness and insomnia. Lomotil should be used with caution in patients with impaired liver function and in patients taking addicting drugs or barbiturates. Lomotil is a brand of diphenoxylate hydrochloride with atropine sulfate; the subtherapeutic amount of atropine is added to discourage deliberate overdosage.

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Precautions and contraindications: Patients with tuberculosis or those who are known to be sensitive to iodides should not be given Pediacof.

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PRESIDENT'S LETTER

You must realize the deep personal gratification that is mine upon assuming the presidency of the Minnesota State Medical Association. My emotions, as you may surmise, are mixed. Owing to my association of the past years with my illustrious predecessors, it is my conviction, however, that they, too, undertook the duties of the office with some concern regarding their own qualifications.

It seems obvious that most persons who find themselves in the office of president must sometimes question their own adequacy. One does not achieve the presidency by unilateral effort. It comes only through the regard and good wishes of one's associates and colleagues. Knowledge of this beneficence on the part of one's friends, and of the responsibility that goes with it, can only lead to misgivings as to one's own fitness, and to the hope that their confidence has not been misplaced.

On the other hand, I have observed that my predecessors have been able to take over their duties with considerable assurance; and the basis for this assurance is easily understood when one examines the structure of our Association.

The Minnesota State Medical Association has existed continuously for well over a century. The Association has not only survived but has grown in all respects over the years of its existence. Time has only added to its strength; and the affairs of the society have always been conducted in a seemly fashion after proper deliberation by qualified authorities. Correct precedents have been set. Appropriate policies have been evolved. Innovations have been orderly.

During my incumbency as president of the Association, you may be assured that there will be no attempt, on my part, to change or to set policy. This function belongs to and is the duty of the Council and the House of Delegates. The latter body, after all, is the final authority for initiating or reversing any action or consideration that arises for deliberation by the Association.

I am aware of the fact that it is my major duty over the next year to see to it that a full interpretation of the policies of the physicians of the state is presented in a fitting manner to the general public. I believe, also, that I can be of help by making it my business to know when, and to whom, any problem may be referred for consideration and, hopefully, for solution.

I hope to be available on Association matters at all times for this purpose, and I shall welcome the opportunity to discuss Association affairs with anyone who is interested in exchanging ideas about the policies, purposes and plans of our organization.

J. P. Medelman M.D.

John P. Medelman, M.D.
President
Minnesota State Medical Association

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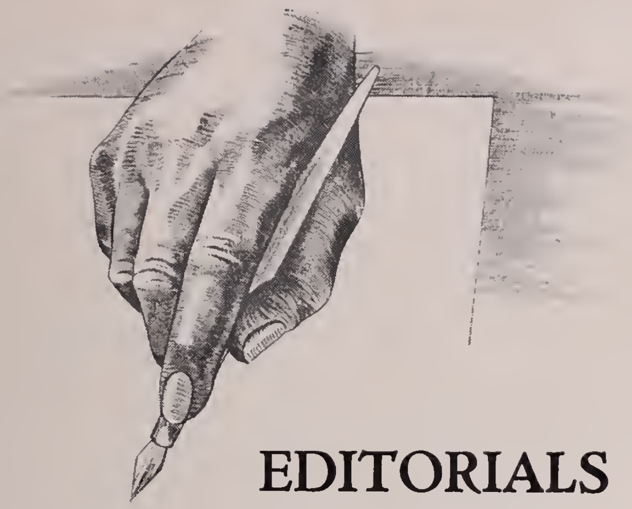


EDITORIALS

Dear Doctors

I am your state medical journal and I have been your constant companion now for 45 years. I trust that the loyalty I have felt for you has been mutual, for I have tried hard to please you. You have grown up and become successful. I too am maturing but must continue to look young. Moreover, I must maintain the intellectual integrity, the specific virtues, and the dedicated service to humanity with which you have imbued me: the high ideals of our ancient heritage. If I have made a few inadvertent errors along the way, overlook them and forgive me.

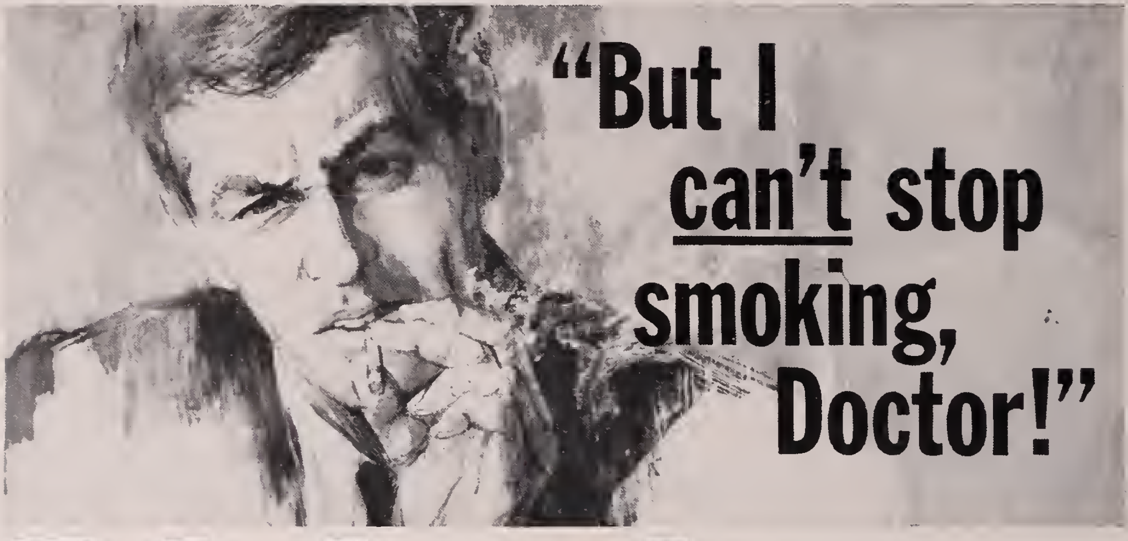
You may have noticed that I have acquired a new face, and as you turn the cover you will note changes in my format also. I have a new printer who is helping to dress me up. My fresh attire costs a bit more but I believe you can afford it.

I am sure you would enjoy seeing the fascinating topics of your eternal shop talk immediately before your eyes — with no pages to rip out in order to get to the heart of your interest. Read me, study me, devote time to me; for you must know that many of your colleagues and associates have burned the midnight oil in order that you might gather my pearls or pick my brains.

After you have studied my scientific content, turn leisurely to my Editorials to become acquainted with some of the thoughts and philosophies of a variety of men who have been interested in your numerous fields of medicine. There is also an opportunity for you to refresh your clinical acumen by reviewing with some very clever gentlemen, the Clinical Path Conference, the Grand Rounds, the Tumor Conference, and the Fracture Conference. These will now become regularly appearing items which you may look for.

From there you are on your own, with abstracts, book reviews, medical economics, organization, personal items, and what not, all of which have a medical background and significance. If from time to time they touch on legal, religious, political, economic, social, or other fields, it is solely for the purpose of providing interesting and relevant information. The only proselytism intended is that of converting you to the idea of being broadly informed. That is my duty.

When your patient says:



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References: 1. Goodman, L. S. and Gilman, A.: The Pharmacological Basis of Therapeutics, New York, Macmillan, 1960, Ed. 2, pp. 620-622; 2. Edmunds, C. W.: J. Pharmacol. and Exper. Therap., 1:27, 1909; 3. Hazard, R. and Savini, E. Gand., 92:471, 1963. 4. Dorsey, J. L.: Ann. Int. Med., 10:628, 1936; 5. Rasmussen, K. B.: Ugeskr.laeger, 118:222, 1956; 6. Ejrup, B.: Sven. lak. Tid., 53:2634, 1956; 7. Jochum, K. and Jost, F.: Munch. med. Wchnschr., 103:618, 1961; 8. Jost, F. and Jochum, K.: Med. Klin., 54:1049, 1959; 9. Smoking and Health, Summary and Report of the Royal College of Physicians of London on Smoking. New York, Pitman, 1962.

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I trust you know who has been supporting me. You have done your share; but so many luxuries have been desirable that I have called upon your many friends. I trust you have not objected. Their names are no secret, for on my left-handed pages, you will note references to their generous and understanding personalities. Though I owe them some degree of loyalty, they never impose themselves upon me against my better judgment.

After an appreciative appraisal of my new format and a profitable perusal of my contents, let me suggest that you either file me away with my predecessors for future reference and research, or start me circulating among your friends to whom I might well be of interest and value. You might join the "Doctor-to-Doctor" venture that will send me to your colleagues abroad who are eager to receive such journals as me. In my May 1963 issue appeared a brief but important item on page 501: Share Your Medical Journals — to which you can refer for details about this worthy and altruistic program.

Minnesota Medicine

Letter to the Editor:

In the November, 1963 issue of MINNESOTA MEDICINE, in the "Curbstone Consultation" section, there is a question relative to a young woman with known mitral stenosis who was functional class I but during pregnancy developed atrial fibrillation and pulmonary congestion. After receiving digitalis, the rhythm reverted to normal and the pregnancy was successfully completed. Her functional capacity was apparently not changed by the pregnancy.

I would like to disagree with at least part of the answer given to this question. I would concur that the digitalis should be continued, but I believe there is no justification for recommending combined right and left heart catheterization with a view in mind of an operation if the catheterization studies should so indicate. The fact that this young woman developed pulmonary congestion in the presence of mitral stenosis, pregnancy, and uncontrolled atrial fibrillation, is neither surprising nor alarming. The important point is that she has a near normal functional capacity when not pregnant and when the rhythm has been controlled. She could not reasonably be expected to have severe mitral stenosis under these circumstances.

There are very definite hazards in the doing of combined right and left heart catheterization. Furthermore, the operation that is currently used for the relief of mitral stenosis is strictly palliative in my opinion and is in no sense curative. It would seem to me that this patient might better be followed by her physician and should her symptoms progress to a functional class III level, further studies would then be indicated.

Paul Winchell, M.D.
University of Minnesota

To wait may encroach upon eternity —

Who said MAGIC doesn't work?

What was once a tooth is now a coin. The smile proves it. This kind of magic works only for children and works best when dad is in on the secret. Some people think that magic loses its power as children grow up. We aren't so sure. Maybe the kind of magic that works for children turns into what adults call faith in the future. Some of this faith plus money growing in a savings account works almost like magic in helping you do the things you want to do. Our current rate on savings is 4% per year . . . earnings credited 4 times a year. Your account is insured for safety.

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CURBSTONE CONSULTATION

Heat Tolerance

QUESTION: I understand that individuals who are constantly exposed to a warm environment develop a tolerance to heat permitting them to carry on work under such circumstances better than a person newly introduced into such an environment. Is this true? If so, is there a physiologic basis to account for acclimatization to heat?

M.D., St. Peter

ANSWER: The mechanism of such adaptation is very complex. An over simplified explanation may be outlined as follows:

Initially there is a contraction of the extra-cellular fluid and plasma volumes due to the large amount of salt lost in the sweat. At the same time there is an increase of the intravascular volume diverted to the skin. A decrease in renal plasma flow occurs and increased aldosterone production is stimulated. As a result urinary sodium may fall virtually to zero. The sweat glands have the ability to decrease the loss of salt through the skin by a marked reduction in the concentration of sodium chloride.

It may take ten to twenty days before the individual is able to establish a new equilibrium because the kidney has the ability to escape from the sodium retention to some extent.

Eventually the individual may be able to perform in a warm environment on a normal salt intake as a result of these various adaptive mechanisms.

Scalene Node Biopsy

QUESTION: Is scalene node biopsy indicated on a routine basis for those patients with suspected or proven bronchogenic carcinoma but without palpable cervical nodes? *M.D., Duluth*

ANSWER: If extrathoracic extension of the disease is considered a sign of inoperability then approximately one of five patients will be spared needless thoracotomy by doing a scalene biopsy even in those cases without palpable nodes. The possibility of securing positive biopsies in cases with nonpalpable scalene nodes is further increased when there is X ray demonstration of mediastinal nodes or a widened carina is found at bronchoscopy.

The person who knows everything has a lot to learn

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FRACTURE—TRAUMA CONFERENCE

Colles' Fracture

Colles' fracture is in the distal radius within one inch of the joint, usually with fracture of the ulnar styloid. The distal articulation of the radius is angulated dorsally from its anatomic position. The fracture may or may not enter the wrist joint.

Mechanism of Injury

Most of the fractures of the distal forearm are due to falling on the outstretched hand. The muscular effort at this time is pronation. As the body weight is transmitted through the hand and wrist, the opposing force is supinating and dorsal angulating. Hyperextension forces cause some crushing of the dorsal portions of the radius and often of the ulna.

Examination

In those individuals with moderate displacement, the diagnosis is obvious. Hematoma in the area of the wrist may be found in injuries of the carpus.

Extensive Angulation

When the angulation is severe, the injury may erroneously be called a dislocation. Dislocation of the radiocarpal joint is rare but can occur in the presence of fractures of the radial and ulnar styloids.

Nerve Dysfunction

Nerve and vessel function are assessed and recorded; commonly there is some median nerve dysfunction within a short time after injury. This is true of violent injuries such as in automobile accidents and in those cases where there is complete dorsal displacement of the distal fragment with over-riding. Deformities with considerable angulation of all tissues of the volar surface of the forearm may show vascular insufficiency.

X rays

The common practice for injury of the wrist includes an X ray of the lower part of the forearm and the carpus and a portion of the metacarpal bones. Better practice would be complete X ray of the forearm including the carpus in suspected injuries about the wrist. From these X rays, classification of the particular injury and a plan for treatment are made.

Continued

Treatment of Colles' Fracture

Imperative surgical measures are dictated by open fractures; less urgency is required in other instances.

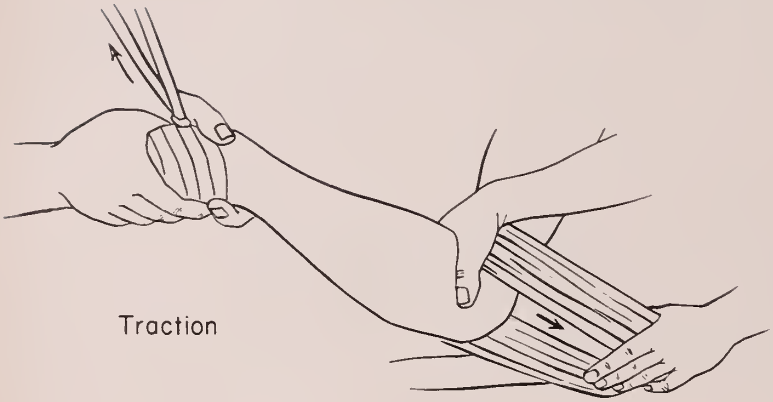


Fig. 1

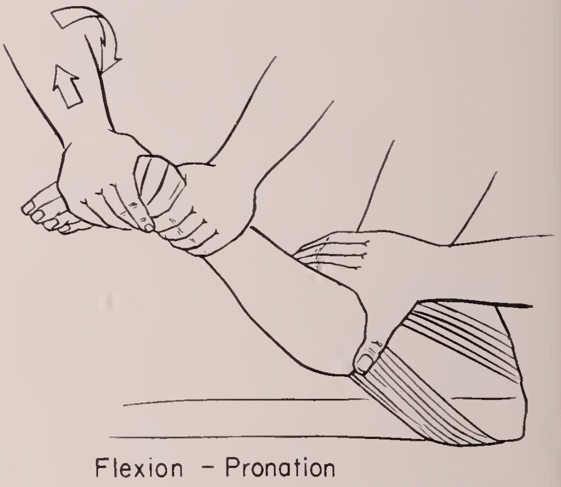


Fig. 2

Immediate Reduction

Where complete dorsal displacement of the distal radius with overriding of the fragments is present in adults, it is suggested that urgent reduction of the fracture be carried out in order to prevent or minimize median nerve palsy.

Emergency treatment for the ordinary Colles' fracture is splinting, elevation, ice packs, analgesia, and sedation. The best splinting is a posterior or anterior molded plaster splint with a nonelastic type of dressing to hold the splint in place. Enzymes to reduce swelling may be used but their value is not certain.

Delayed Reduction

The author prefers to reduce the average Colles' fracture one or two days after injury. During this time the soft tissues have stabilized regarding swelling. The wrist has been held more or less straight, preventing further embarrassment of the median nerve and the structures in the volar tunnel. There is less postoperative pain and stiffness following delayed reduction, and there are few instances where the plaster must be split to relieve pain or swelling; also fewer secondary manipulations are necessary.

Anesthesia

Local anesthesia may be used to advantage within one or two days of injury. Prereduction sedation is an advantage but not an essential. General anesthesia may be used.

Methods of Manipulation

Traction (Fig. 1)

Traction, palmar angulation, and pronation are the three fundamental maneuvers in manipulation of the ordinary Colles' fracture. When the fracture is dorsally angulated with impaction of the distal cortex, and the anterior cortex is in contact, flexion and pronation are sufficient for good reduction. With shortening of the cortices or overriding, traction becomes of primary importance.

Flexion—Pronation (Fig. 2)

Following restoration of length, flexion and pronation are accomplished. The reason for flexion seems apparent with the impaction and comminution of the dorsal cortex of the radius. Most commonly overlooked is the need for pronation. Pronation of the hand and wrist on the forearm is frequently the only way in which a complete anatomic reduction may be accomplished in the displaced and overriding fracture in which good general alignment has been achieved by traction and flexion. Flexion and pronation may be performed with the same maneuver.

Reduction is facilitated by the use of a sling about the patient's upper arm secured to the operating table providing countertraction. Traction on the patient's wrist is by a hitch which is looped about the shoulder or waist of the operator for bodily force. These slings at the arm and wrist free the operator's hands for manipulation. If one encounters a workman with stronger arms than the operator, general anethesia should be used, since these fragments may not be pulled down without good relaxation.

X rays

X rays are taken in the lateral and anteroposterior position to determine the adequacy of the reduction. The fracture should not be shifted during the period of waiting for X rays.

Criteria for Adequate Reduction

The reduction can be measured by the degree of volar angulation of the distal articular surface, usually 13° to 17° (Fig. 3). A more accurate measurement of reduction is the continuous line of the volar surface of the radius. Radial length may be analyzed in the same way by following the cortical outline on the posterioanterior X ray (Fig. 3).

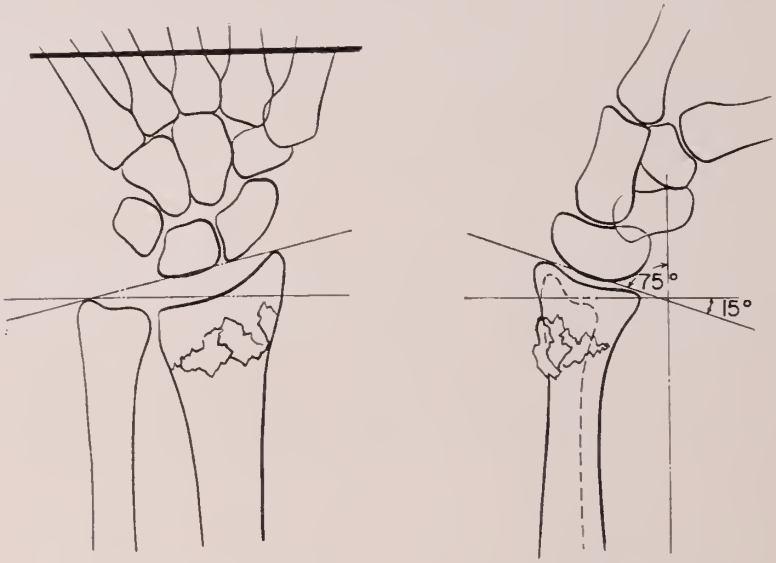
Any distal radius fractures in the adult in which the articular surface is at right angles, or less, to the distal radius probably should be reduced. If the original displacement is not corrected, they leave a deformed wrist.

Cast Immobilization

The author prefers the long arm cast with the elbow at right angles and the wrist in moderate flexion (30 to 40°) and moderate pronation. It is the impression that there is less fracture slippage in the long arm plaster. When the elbow is not immobilized, pronation and supination may dislodge unstable distal radius fractures. If splints are applied to the forearm, a nonelastic dressing such as

Continued

"Kling" or other bandage is utilized, rather than the elastic bandage which has an undesirable continuous compressing force on the tissues. There is less swelling by this method than with the use of an elastic bandage.



Radial Length and Angle Restored

Volar Angle Restored

Fig. 3

Postreduction Care

The arm should be elevated for two or three days after reduction. The long arm cast should be maintained for four weeks, replacing it with the short arm cast with the wrist in a more neutral position for two more weeks. X rays are taken at the end of one and two weeks and then again at four weeks to be sure that the shortening of the radius is not excessive or the loss of angulation of the articular surface more than acceptable for good clinical results.

Shortening

Many of these fractures inevitably shorten, due to the comminution of the bone. Up to one-eighth inch shortening and loss of the volar angulation to the neutral position are acceptable for good cosmetic and functional results.

Dorsal Angulation

When the articular surface angulates dorsally beyond a right angle to the long axis of the forearm, the function and appearance are less than desirable. All patients are told that these fractures are unstable and may shift in the plaster with the reduction of swelling and passage of time.

Motion

Finger exercise is started the day of injury. Motion of the fingers is not a factor in the loss of position of these fractures. Shoulder exercises should be done a dozen times a day with the hand and arm being overhead and behind the back to prevent stiffness of the shoulder. *(To be continued)*

Kenath Sponsel, M.D.
Minneapolis, Minn.

Learn from the mistakes of others — you can't live long enough to make them all yourself. — Intelligencer, Doylestown, Pa.

TUMOR CONFERENCE

Carotid Body Tumor Presenting in the Oropharynx

A tumor arising from the carotid body usually is benign and presents itself as a slow-growing mass just anterior to, or beneath, the sternocleidomastoid muscle in the anterior triangle of the neck. Although in certain large series,[1,2] and sporadically in the surgical literature, there are reported instances of metastases from these lesions, the usual course is for gradual enlargement over a period of years. Unfortunately, by its mere size or by impingement on surrounding important structures, the tumor can cause great morbidity and even death. On occasion, as in the case reported here, the mass can present itself in the oropharynx and lead to other complications.

Case History

A 56-year-old female, was admitted to Roswell Park Memorial Institute in September of 1962. She had been in good health until May of 1962, at which time she was found to have a mass in the region of her right tonsil during a routine physical examination. A biopsy was performed on May 24, 1962, at the Warsaw, New York hospital. There was severe hemorrhage from the biopsy site and two units of blood were given. Her right tonsil was removed at the Buffalo General Hospital on July 5, 1962, but on histologic examination it was found to be normal.

On admission she was found to have a large submucosal mass protruding from the right retropharyngeal area distorting the posterior tonsillar pillar and pushing it forward. She was presented to the Head and Neck Conference and a decision was made to excise the mass through a cervical incision.

At surgery the mass itself was found to be firm and incorporated in a complex entanglement of dilated tortuous veins carrying what appeared to be arterialized blood. It was intimately associated with the carotid artery at its bifurcation. An arteriogram performed at this time revealed the mass to be richly vascularized and displacing, but seemingly not involving the artery itself. The veins were carefully ligated and divided; but, as the tumor itself was exposed, each small vessel seemed to bleed furiously. Finally, with sharp and blunt dissection, the mass was dissected free of the vessels. It measured 3 x 2.5 cm. Final pathologic diagnosis was carotid body tumor.

Circumscribed submucosal lesions in the oropharynx should be excised rather than biopsied. The difficulty in obtaining adequate exposure and the possibility of hemorrhage and aspiration makes this a major procedure. Careful thought must be given to the origin of these tumors preoperatively; lesions arising from lateral neck structures (i.e., deep lobe of parotid gland, carotid body, submaxillary gland) are better exposed through the neck than the oropharynx and there is less likelihood of damaging contiguous vessels or nerves. The steps in removal of carotid body tumors

Continued

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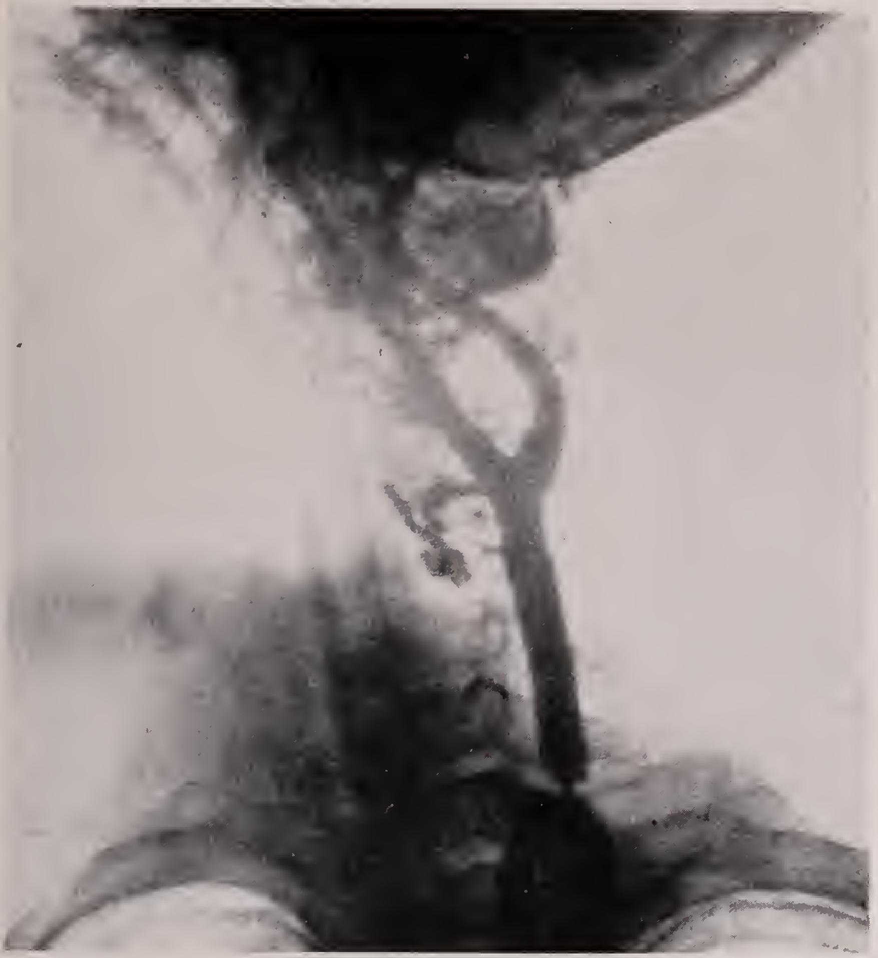

Arteriogram at surgery demonstrating richly vascularized carotid body tumor.

will not be discussed in detail, but with present-day vascular techniques the tumor can be removed with a segment of artery and flow maintained during reconstruction of the carotid artery by means of a polyethylene shunt. Modern vascular surgery has indeed improved the outlook for patients suffering from this potentially lethal tumor.

Harrison H. Farley, M.D.
Minneapolis, Minn.

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Men have lost sight of distant horizons. Nobody writes for humanity, for civilization; they write for their country, their sect; to amuse their friends or annoy their enemies.—George Norman Douglas

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INDUSTRIAL MEDICINE

Physical Examinations

A physical examination program is one of the basic features of an Industrial Health Service. It can be the cornerstone around which to build the other elements of the program or it can be the stumbling block which nullifies the Service.[7]

The secret of success is wrapped up in one word — attitude, and there is one person whose attitude matters most — the examining physician. The attitudes of management and labor and individual employes are important, but they are subject to change, and the direction of that change is utterly dependent on the attitude of the examining physician. The examining physician then holds in his own hands the power to make or break a physical examination program.

A bored, unenthusiastic attitude on the part of the examining physician will lead to rumors of incompetence, lack of confidence and lukewarm support of the Health Service. A hasty, perfunctory examination generates the attitude that the examination is of little value and that the employe is wasting his time and the employer his money. An examination performed without the usual courtesies and gentleness creates in the workman the impression that he as an individual is considered a nonentity, unimportant in the grist of the mill. An examination conducted with thoroughness, but which leaves out a discussion of the findings with the employe sends the workman away with the impression that the doctor has sold out to the employer and is only trying to find a basis to deny him a job or deprive him of advancement, or to keep him off the company pension or insurance plan.

The examining physician should remember that in industrial medical practice he always has to reckon with organized labor. He, of course, is working neither for nor against labor, but he must beware of appearing to represent and support management's interests. Organized labor is fearful of the misuse of physical examinations by management, because labor cannot protect a man from discharge if he is physically unfit to work. This reflection on the integrity of medical examiners is the concern of all doctors, because physical examinations in industry cannot very well be misused unless the examining physician is a party to it. In Wisconsin the feeling on this matter has resulted in writing into the workmen's compensation law penalties for employers who apply physical examinations in an oppressive manner to reject or discharge workers.[3]

When a doctor practicing industrial medicine enjoys the respect and confidence of the employes, he naturally is impelled to conduct careful and conscientious physical examinations. Then, too, when the doctor approaches the examination with the attitude that it is being conducted primarily for the benefit of the workman, he as a matter of course discusses the findings with the employe. Furthermore, finding a disease condition is recognized to be only the first step. The doctor who cares will quite naturally follow through and get the employe under treatment by his private physician.

To maintain the normal doctor-patient relationship in industrial medicine, it is necessary to preserve, so far as possible, the usual professional confidences. The workman should be made to feel that what he reveals to the physician remains in the medical files and is not available to management or his fellow workmen.

There is, of course, another side to the question of confidential medical records. Many employers or personnel men feel that they need to know the complete story about an employe's health. They argue that the company is held, by the compensation law, to be responsible in the aggravation of a pre-existing condition and they contend that they cannot assume that burden without knowing its nature and significance. There is some justification for this contention, and when the doctor also feels that the employer should be more definitely informed than the code system permits, he should explain the situation frankly to the employe and ask for his

Continued

written permission to reveal the information. Of course, where the handicap is one which an ordinary observer can see, it is not a professional confidence.

It is generally agreed by authorities in industrial medicine that some kind of a code system should be used to convey to the Personnel Department the workman's capacity and limitations without giving specific medical information. An example of such a code is outlined below.

A_1—Meaning—physically and mentally fit for any work in the plant and having no impairments.

A_2—Meaning—possessing some minor, nonprogressive condition, but still physically and mentally fit for any work in the plant.

B_1—Meaning—possessing some impairment or condition which limits his activity or makes it advisable to avoid certain areas or certain types of work. (What he is to avoid must be specifically stated.)

B_2—Meaning—temporarily unemployable. When this classification is used it means that the applicant is suffering from some temporary ailment or correctable condition which renders him unfit for employment until it is relieved or removed. An applicant classified as B_2 would be subject to re-examination and reclassification when he again applied for work.

C—Meaning—unfit physically or mentally for employment at any job in the industry.

The pre-employment physical examination should be employed not primarily as a means of selecting only first class risks for the company, but as an opportunity for the examining doctor to assist the company in the placement of employes into jobs for which they are physically and mentally suited. When such an attitude is taken, very few applicants need be rejected. However, even when an applicant must be rejected, the examining physician should explain to the rejectee just why the company cannot use him and should urge him to seek medical care through his private physician.

Examining physicians, especially those who do not employ a work-capacity analysis, should have an intimate knowledge of the jobs to be filled in the plants which they serve. There is no better way to become familiar with the job requirements of a factory than by making frequent and regular inspection tours. This is one of the reasons why a physician who performs his physical examinations on the factory premises has an advantage.

Several types of physical examinations are commonly conducted for industry.

1. *Pre-employment or Preplacement Examinations.*

2. *Periodic Examinations.* — These are routine repeat physical examinations performed at regular intervals according to an established policy or plan. Included are general workmen, executives, and selected groups who may be subjected to extra strain or hazardous occupations. The interval between examinations will vary with the circumstances surrounding the job.

3. *Transfer examinations.*—Further examination is sometimes necessary when an employe is being considered for transfer to another job or promotion to greater responsibility.

4. *Termination Examinations.* — Some companies, because of the nature of their work and their continuing responsibility for such things as silicosis, may require a physical examination when the employment is terminated.

5. *Return to Work Examinations.* — Some accidents or sicknesses alter an employe's suitability for employment at the same job. In such cases another examination is required for reclassification.

6. *Special Examinations.* — Such examinations are not routine but are conducted only when necessary for diagnosis. These examinations are requested by the employe himself or someone else on the supervisory staff, or the employe is called in by the health service for a follow-up of a known condition.

When an examination is performed, for whatever purpose, it should be well done and a careful record made. There are many features which deserve special emphasis which will vary with the industry. Some factories may emphasize vision tests. Some heavy industries may need to pay special attention to joints, feet, varicose veins, back strength and function, hernia and so on. Most physicals include personality appraisal, an X ray of the chest, a certain amount of laboratory work, and a serological test for syphilis.

Usually some of the routine technical tests are performed by a nurse or trained layman. The physical examination, however, should be conducted only by a physician.

The practice of having a nurse take a history of past illnesses, perform certain laboratory tests, and conduct a cursory inspection as a substitute for a physician's physical examination, I believe, is not in the best interests of industrial medicine and should be discouraged.

A complete history of previous occupations is especially important as a guide to later disease developments and to protect the company from unjust claims which may relate to a previous occupation.

Because of the increasing interest in occupational loss of hearing, it is becoming important to make a careful record of hearing acuity at the time of the original pre-employment examination and at regular intervals for men employed in noisy occupations. It may very well be that the time is not far off when anything less than an audiometer test will be considered inadequate.

The industrial physician should always remember that his function is to help and protect the individual employe. In this respect he should be a champion of the obviously handicapped. He should seek first proper placement of each and then maintain a sustained interest and follow-up. The industrial physician should honestly question the commonly accepted reasons for excluding an applicant from employment and remember that, as a citizen, a physician has a moral obligation to the individual and to society to assist and encourage everyone to be self supporting. Proper placement is often more difficult and time consuming than the easy road of rejection, but it pays off in employe independence, employe faithfulness and loyalty to the company, and in personal satisfaction for the industrial physician.

W. E. Park, M.D.
Committee on Occupational Health
Minnesota Medical Association

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Galen's Materia Medica*

Archigene's Prescriptions for Toothache

Hold for some time in the mouth a frog boiled in water and vinegar, or a dog's tooth, burnt, pulverized and boiled in vinegar. Cavities may be filled with toasted earthworms or spiders' eggs diluted with unguent of nard.** Teething infants are benefited if their gums are moistened with dog's milk or anointed with hare's brains.

A cooked black chameleon performs the double duty of curing toothache and killing mice. To extract a tooth in the upper jaw, surround it with the worms found in the tops of cabbage. For the lower tooth, use the worms on the lower part of the cabbage leaves.

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*Thorndike, Lynn — see Minn Med Oct. '63.
**Alpine plant valued as medicine in perfume.

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GRAND ROUNDS

Pernicious Anemia

Neurological Manifestations*

Pernicious anemia is a chronic disease characterized by:

1. Achylia gastrica (achlorhydria)
2. Insidious onset
3. Macrocytic anemia
4. GI disturbances
5. CNS disturbances
6. Increased blood destruction
7. Response to specific therapy (Vitamin B12)

History

The clinical features of pernicious anemia were described by Addison in 1855. The changes in bone marrow were discovered by W. Pepper and J. Cohnheim. The histological changes in the blood were described by Ehrlich. The possible primary role of the stomach in the etiology of pernicious anemia was suggested by Fenwick in 1880. Lichtheim called attention to the changes in the spinal cord in 1887. The hemolytic concept of pernicious anemia is based on the results of William Hunter's research, 1888. Minot and Murphy in 1926 demonstrated conclusively the value of liver therapy. Castle's experiments clarified the relationship between achylia gastrica and the hematopoietic effectiveness of the liver.

Incidence

The incidence of subacute combined degeneration of the spinal cord parallels that of pernicious anemia which is estimated to be 35 cases per 100,000 population in the temperate zone of America and Europe. It occurs in all races but is most common in blue-eyed individuals of the Nordic race, whose hair has turned prematurely gray and who have broad facies and a large body frame. The familial incidence is estimated at about 18 percent.

Race

Pernicious anemia is a disease chiefly of the temperate zone and the white race. It is relatively uncommon in Jews and rare in Orientals. It has been said to occur seldom if ever in full-blooded Negroes, but of 329 cases admitted between 1925-1940 to the wards of the Johns Hopkins Hospital, where the admission of white and colored patients was about 3:1, 33 were Negro.

Age

Pernicious anemia is a disease of late adult life, being most frequent after forty years of age and increasing in frequency as age advances. It is rare under 30 years of age and extremely unusual in children. Of a total of 1,532 cases of pernicious anemia only four were below the age of twenty years.

Sex

In the United States and England males have been more frequently the

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*Presented as a Medical Grand Rounds at the Mt. Sinai Hospital, Minneapolis, Minnesota.

Continued

victim of this disease, but in Germany and the Scandinavian countries the opposite has been recorded.

In Cabot's series (1908) the disease affected males twice as often as females, whereas in an Edinburgh series of 600 cases seen during the period 1938–1956 females were affected twice as often as males. A recent analysis of 223 cases examined in Glasgow showed an incidence of three females to one male.

Symptoms

The onset of the illness in the great majority of cases of pernicious anemia is extremely insidious. This is as true today as it was 50 years ago. Table 1 shows that the two symptoms most commonly encountered in pernicious anemia, both in the pre-liver era and at the present time are general weakness and tiredness, and dyspnea on effort. The third most frequent symptom is the feeling of numbness and tingling in the hands and feet. This symptom, however, occurs much less frequently now (38% of cases) than in did 50 years ago (approximately 100% of cases).

TABLE 1
Symptoms

	Pre-Liver Series		Edinburgh Series 1944-56 Davidson
	1908 Cabot Boston	1923 Panton London	
No. of cases	1200	117	250
Weakness and Tiredness	96%	91%	90%
Dyspnea	88%	—	70%
Sore tongue	43% of 372 cases	24% of 34 cases	25%
Diarrhea	51%	26%	9%
Constipation	35%	—	16%
Paraesthesia	100%	—	38%

Signs

A comparison of the signs encountered is shown in Table 2.

TABLE 2
Signs

	Pre-Liver Series		Edinburgh Series 1944-56 Davidson
	1908 Cabot Boston	1923 Panton London	
No. of cases	1200	117	250
Fever	79%	71%	22%
"Icterus"	most cases	—	uncommon
Acute glossitis (red and ulcerated)	42% (of 372 cases)	—	5%
Chronic atrophic glossitis (pale and smooth)	—	—	64%
Splenomegally	27%	18%	8%
Spinal cord damage	11%	—	7%
Ataxic type	7%	—	6%
Spastic type	4%	—	1%
Peripheral blood			
2 million RBC/cmm.	86%	average	58%
1 million RBC/cmm.	21%	1.39 million	1%

Neurological Symptoms

Neurological symptoms begin in most cases after the anemia has been demonstrated, and after somatic symptoms of fatigability, weakness, changes in skin color and glossitis are obvious. Sometimes nervous manifestations suggestive of combined cord degeneration appear before the systemic disease is apparent, or before blood changes can be demonstrated.

Spinal Cord Degeneration

Degeneration of the spinal cord develops in about 80 percent of the patients whose earliest signs of pernicious anemia include tingling and numbness. Those patients in whom paresthesias develop during the course of anemia, and not at its onset, are far less liable to develop signs of involvement of the spinal cord. These paresthesias are the result of involvement of the peripheral nerves, and only 20 percent of these patients become afflicted with subacute combined cord degeneration. It was originally assumed that the neurological lesions in pernicious anemia were confined to the spinal cord, but later studies demonstrated that peripheral nerve degeneration also occurs. Numbness, impaired sensation of the "stocking" type, as well as hyperesthesia, may result from peripheral nerve changes. Changes in peripheral motor nerves, however, with resulting motor paralysis and muscular atrophy are unusual. Two groups of symptoms may be observed with typical degeneration of the spinal cord. One is referable to posterior columns, the other to the lateral descending tracts. Symptoms from these two sources may appear together, isolated or serially.

Paresthesia

Numbness and tingling of the distal portions of the upper extremities are the characteristic presenting symptoms in nearly all cases. As the disease advances the proximal portions of the extremities become involved and the patient experiences a girdle-like sensation in the thorax. This is not ordinarily a painful sensation but is usually described by the patient as an uncomfortable, annoying feeling of "pins and needles."

Objective sensory loss is greatest in the sphere of proprioception and the patient's hands become clumsy because of difficulty in sense of position. Patients are not aware of the exact position of their extremities. Co-ordination in finer finger movements is deficient. The patient walks on a broad base with stiff-legged motions, sways from side to side in an ataxic fashion, and the Romberg test is usually positive. Tactile sensation, although usually diminished, is rarely absent. The posterior column symptoms may be present in their entirety in severe cases, but all combinations and gradations are to be found.

Locomotion

Difficulties in locomotion may be due to the severe sensory loss experienced by the patient, or to involvement of the corticospinal and other pathways. Weakness of the lower extremities is a symptom in practically every case. The deep reflexes may be diminished or absent with hypotonia and flaccidity of the extremities, or they may be hyperactive. The abdominal reflexes are usually absent. The response to plantar stimulation is extensor in practically all cases.

The picture may vary from time to time in the same patient. The lesions in the peripheral nerves are often reversible. With improvement of these lesions and existence of degeneration of the lateral columns, muscular flaccidity and areflexia may give way to spasticity and hyperreflexia.

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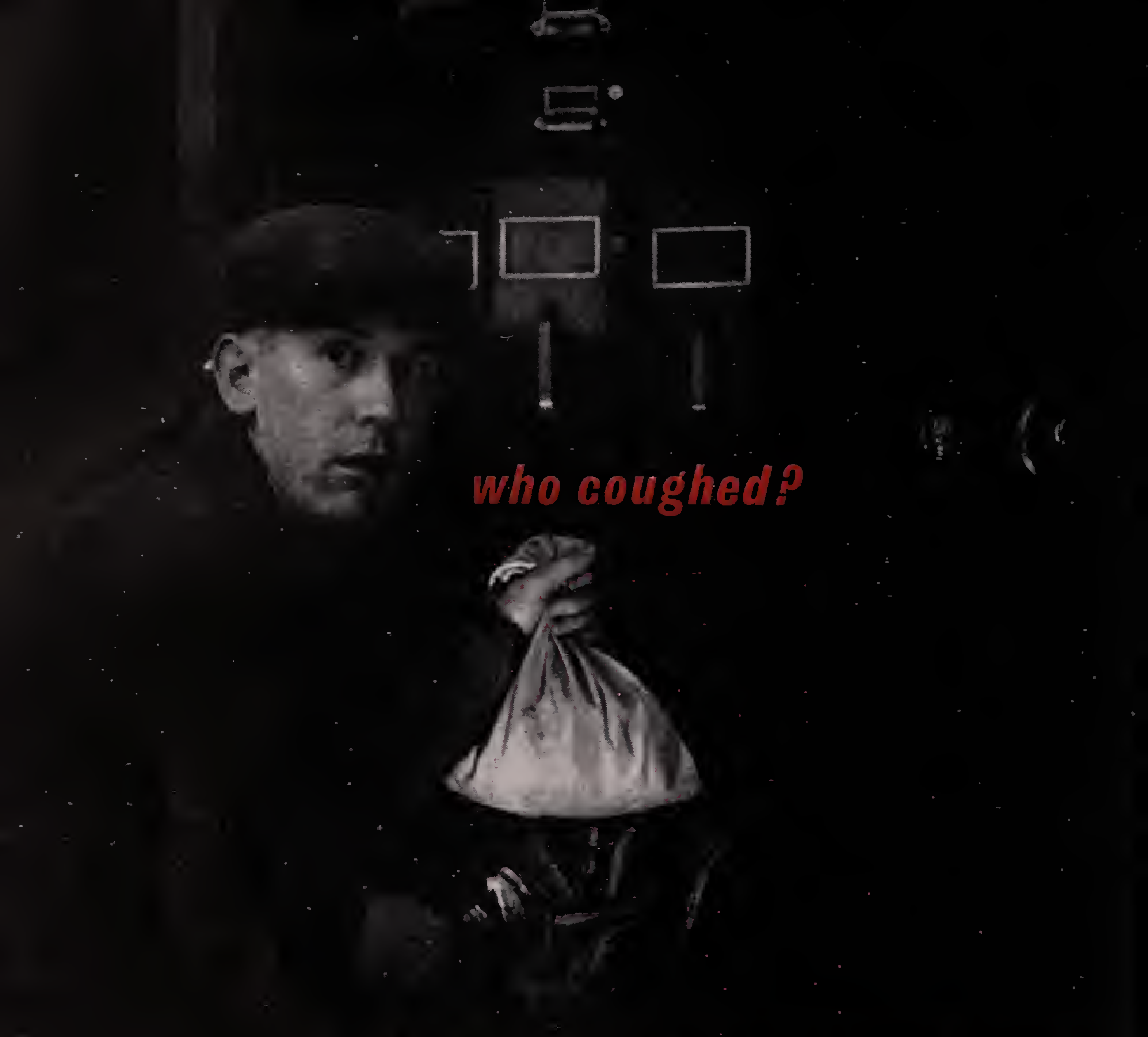
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Homatropine methylbromide 1.5 mg.		
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INDICATIONS: For both productive and nonproductive cough. For relief of symptoms in tracheitis, bronchitis, pneumonia, pharyngitis, bronchial asthma, pertussis, and allied conditions; cough associated with allergy; in general, whenever cough medication is indicated.

DOSAGE: Average adult dose—1 teaspoonful after meals and at bedtime with food. Children 6 to 12 years, ½ teaspoonful; 3 to 6 years, ¼ teaspoonful; 1 to 3 years, 10 drops; 6 months to 1 year, 5 drops; after meals and at bedtime. On oral Rx where state laws permit. U.S. Pat. 2,630,400.

CAUTION: Should be used with caution in patients with known idiosyncrasies to phenylephrine HCl and in patients with moderate or severe hypertension, hyperthyroidism or advanced arteriosclerosis. In these patients use should not exceed three days. Hycomine Syrup is generally well tolerated but in some patients drowsiness, dizziness or nausea may occur. May be habit-forming.

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Involvement of the sphincters of the bladder and rectum appears as the disease advances and impotence may occur. It is a clinical rule of thumb at a New York hospital, on the basis of the observation of more than 60 cases of pernicious anemia, that when extensor plantar responses are present or when there is impairment of vesicle function, complete resolution of the neurological signs is unlikely, no matter how assiduous the replacement vitamin therapy.

Mental Symptoms

Mental symptoms are occasionally encountered. Pfeiffer, in 1915, reported the first case of pernicious anemia in which mental symptoms were prominent. They range from states of depression accompanied by loss of mental energy to definite psychosis. They, like the nervous symptoms, may precede the characteristic changes in the blood by many months. Holmes reported a series of 14 cases of Vitamin B12 deficiency, in which the patients had well marked cerebral symptoms. In all but two cases the mental symptoms disappeared or were greatly improved after intensive treatment. Early diagnosis, though of utmost importance, is at times difficult, because the cerebral manifestations may occur in the presence of a completely normal blood picture and bone marrow. Even when anemia is present there may be no correlation between the degree of anemia and the severity of the cerebral manifestations. Irreversibility may result if one awaits the development of overt hematological signs before the institution of therapy.

Pathology

Subacute combined degeneration of the spinal cord associated with pernicious anemia affects particularly the thoracic and lumbar portions of the cord but may involve the entire length. Anatomically the disease is imperfectly named because damage to the peripheral nerves and the brain are often found in addition to the changes in the spinal cord. Clinically the syndrome is not specific for pernicious anemia, since similar combined degeneration of the spinal cord, lesions of the peripheral nerves and foci of cerebral degeneration occur occasionally with many other systemic conditions. Yet the complete syndrome which will be described in detail is caused only by pernicious anemia. This picture is distinctly different from that described in ergotism, pellagra, syphilis, arteriosclerosis and cachectic diseases; all of these may be associated with clinical evidence of degeneration of the posterior and lateral columns of the spinal cord, however.

Terminology

Richmond and Stanley (1957) suggested that the name subacute combined degeneration of the spinal cord should be discarded for the following reasons:

1. The disease begins insidiously and not subacutely.

2. The combination of lesions in the posterior and lateral tract is frequently absent.

3. The name is cumbersome; and finally it does not take into account the fact that peripheral neuritis develops first and is almost always associated with degeneration in the cord, and that in a small proportion of cases there are mental changes due to brain damage.

Vitamin B12 Neuropathy

Accordingly they suggest that the title "Vitamin B12 Neuropathy" should be used to describe the neurological manifestations. Under rare circumstances the entire circumference of the cord may be demyelinated, giving a transverse

Continued

syndrome. The posterior columns vary in involvement. The column of Goll is more affected than that of Burdach. as a rule. There may be severe involvement of the posterior columns and little of the lateral, or vice-versa. The peripheral nerves have been found to show degeneration in some cases. The lesions are symmetrical and involve the posterior column, crossed and direct pyramidal tracts, and the cerebellar tract. In the early stages and during remissions they are confined to the dorsal columns. They can be seen as translucent patches with the naked eye. This is not a system disease. The lesions are formed by the fusion of many small patches. The process is most intense near the periphery of the cord. At first there is a spongy breakdown of these areas, followed later by gliosis.

Nerve Cell Changes

Changes in the nerve cells are usually not outstanding. Microscopically, the areas of degeneration show loss of myelin and axis cylinders with only a mild tendency to gliosis in the affected regions. There is a tendency to repair, as shown by gliosis in pernicious anemia patients treated by liver injections. The degenerated areas have a lace-like, spongy appearance which is quite characteristic of the disorder. The anterior horn of the spinal cord usually escapes but hemorrhages are occasionally found within them.

Cerebral Cortex Changes

The cerebral cortex shows evidence of damage in some cases. Pathological studies by Adams and Kubic revealed that the important pathological changes consisted of a diffuse though uneven degeneration of white matter with relatively little or no proliferation of fibrous glia. Microscopic changes were found in the central and convolutional white matter of the cerebral hemispheres, in the cerebellar peduncle, and in the optic tracts near the chiasma. The microscopic changes described were essentially the same as those found in subacute degeneration of the spinal cord. These authors also noted an increase of the number of astrocytes and oliogodendrocytes throughout the white matter. This change was most marked just beneath the cortical gray matter.

Sequellae

To date there have been no authentic reports of cases of subacute degeneration of the brain which have not been associated with spinal cord lesions. This pathological process is unique and easily distinguishable from pellagra and other diseases involving the cerebral white matter.

Pellagra

In subacute degeneration there is uneven degeneration of the fascicular gracilis, while in pellagra there is degeneration throughout.

The degeneration of white matter is prominent, while there is none in pellagra.

There is lack of nerve cell involvement as contrasted with pellagra where the anterior horn cells and large pyramidal cells are moderately involved.

Retrobulbar Neuritis

Retrobulbar neuritis is a rare, though well-recognized complication of pernicious anemia, and may be a presenting feature or may arise during the course of the disease. No satisfactory explanation has as yet been given why only some patients develop this condition. There is an overwhelming male preponderance. Of 29 cases reported in the literature, 26 were males. Yet in pernicious anemia and subacute combined degeneration males and females are equally affected.

Amblyopia

Turner noted that the development of amblyopia in patients with pernicious anemia was not related to the duration of the disease, to the presence or degree of anemia, or to the neurological involvement. In about one quarter of the patients there was no anemia and in one sixth of the patients there was no evidence of subacute combined degeneration. Retrobulbar neuritis may arise in the prepernicious anemia state, in which there is achlorhydria with gastric atrophy, poor absorption of Vitamin B12 corrected by intrinsic factor, and a low, or low-normal serum Vitamin B12 level without anemia. Such patients may later develop pernicious anemia. This evidence suggests that there must be an additional factor responsible for the development of retrobulbar neuritis in pernicious anemia and in the prepernicious anemia state which is far more common in males than females, and which, acting alone, does not cause anemia or subacute combined degeneration. Freeman and Heaton believe that smoking is this factor, the optic nerves being rendered unduly sensitive to the toxic effects of tobacco owing to Vitamin B12 deficiency. Leishman in 1952 indicated that tobacco amblyopia and pernicious anemia coexist in the same subject more often than can be accounted for by pure chance. He found that three of his 15 cases of tobacco amblyopia also had pernicious anemia and an additional seven cases of pernicious anemia were found among the records of 60 patients with tobacco amblyopia. It is known, however, that ½ ounce of tobacco a week or 10 cigarettes a day are quite enough to produce tobacco amblyopia under certain conditions, such as malnutrition or excessive consumption of alcohol, and withdrawal of tobacco does not always result in the arrest of the amblyopia.

Tobacco Amblyopia

In 13 patients with tobacco amblyopia the serum Vitamin B12 was significantly lower than that of normal controls. Other manifestations of Vitamin B12 deficiency may be absent, because in pipe smokers and heavy cigarette smokers amblyopia may precede the onset of anemia, glossitis neurological involvement, or a megaloblastic bone marrow by months or even years. Pipe-smoking is much more liable to produce amblyopia than cigarette-smoking.

In retrobulbar neuritis of pernicious anemia the histological findings in the optic nerves are similar to those observed in tobacco amblyopia. Areas of degeneration of both optic nerves, with considerable proliferation of the neuralgia and round cell infiltration in the tissues and around the blood vessels have been described in both conditions.

Pathogenesis

Decrease in Cerebral Metabolism

The pathological degenerative process appears to be related to a decrease in the cerebral metabolism as a result of a deficiency state rather than as a result of the anemia per se. Scheinberg, in 1951, estimated the oxygen consumption of the brain by the nitrous oxide method in 16 patients with pernicious anemia. He divided the patients into two groups, those with a hemoglobin level above seven and those with a hemoglobin level below 7 gm%. He found consistently low

Continued

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values of cerebral O_2 consumption in patients with cerebral manifestations of pernicious anemia as compared to normal controls and those with secondary anemia (blood loss). There was no correlation between the degree of anemia and the reduction in the cerebral metabolism in patients with a hemoglobin level greater than 7 gm%. There was, however, good correlation between the degree of mental status aberration and the degree of reduction of cerebral metabolism.

Folic Acid

At least eight cases of pernicious anemia are reported in which signs and symptoms have been altered by the ingestion of multivitamin capsules containing folic acid. Heinle and Welch speculated that folic acid not only failed to prevent neurological lesions but might precipitate their appearance.

In one study folic acid lowered the serum Vitamin B12 level in 18 of 27 patients receiving Vitamin B12 injections. The biochemistry of Vitamin B12 and folic acid, although not completely understood, is helpful in explaining how Vitamin B12 can correct both the hematologic and neurologic disorders of pernicious anemia and folic acid only the former.

Desoxy — Nucleic Acid and Ribose — Nucleic Acid

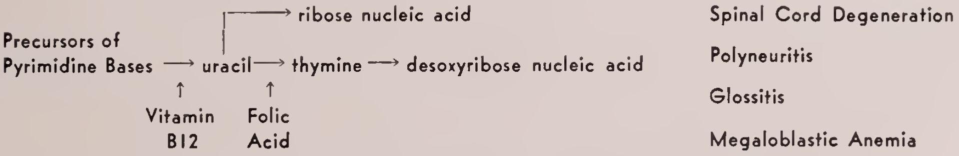
Vitamin B12 and folic acid are essential elements in the synthesis of nucleoprotein. Jukes et al. proposed that Vitamin B12 and folic acid acted as coenzymes at different stages in the production of nucleoproteins. It is postulated by Nieweg et al. that although they work at different stages of synthesis, folic acid is concerned only with the formation of desoxyribose nucleic acid, whereas Vitamin B12 is essential for both desoxy nucleic-acid and ribose nucleic-acid production.

Desoxy nucleic acid is found only in nuclei and chromosomes, when the cell is divided, necessitating a doubling of chromosomal material. Desoxy nucleic-acid synthesis must increase if proper mitosis is to occur. Any lack of Vitamin B12 or folic acid will disrupt this process. The tissues in which rapid turnover and active cell division are taking place will be most affected, and these include the hematopoietic and gastrointestinal systems. Failure to meet the demand for cellular productivity results in megaloblastic anemia, leukopenia and glossitis, the triad seen in Vitamin B12 or true states of folic-acid deficiency.

Ribose nucleic acid contains cytosin and uracil and is found only in the cytoplasm and nucleolus. Neural tissue where cell division is infrequent contains high quantities of ribose nucleic acid.

Desoxy nucleic-acid turnover is low. Folic acid has little effect on ribose nucleic-acid synthesis, and consequently when it is used alone in the treatment of pernicious anemia, neural tissue integrity will fail. Vitamin B12 is required for the production of ribose nucleic acid.

Nucleoprotein Synthesis



The role of Vitamin B12 and folic acid in nucleoprotein synthesis.

Vitamin B12 acting earlier in the biochemical sequence has an essential function in the production of desoxy nucleic acid and ribose nucleic acid, whereas

Continued

folic acid can be effective only in desoxy nucleic acid synthesis. This concept explains why the requirements for Vitamin B12 are increased in folic-acid deficiency, why nothing is to be gained from the use of both folic acid and Vitamin B12 in pernicious anemia, and why Vitamin B12 level is decreased by the administration of folic acid. Most important, it makes clear why Vitamin B12 and not folic acid is the treatment of choice for pernicious anemia.

Diagnosis

The clinical features of subacute combined degeneration of the anemia type are characterized by gradual onset with paresthesia, associated with ataxia and paraplegia, both well marked, with paraplegia and slight ataxia, or with ataxia and slight pyramidal tract involvement (Babinski's sign). The number of possible combinations is great, the signs depending on the degree of involvement of the posterior and lateral columns. Similar types of syndromes with involvement of posterior and lateral columns may be found in multiple sclerosis, syphilis, Friedreich's ataxia, lead poisoning, amyotrophic lateral sclerosis, arteriosclerosis, leukemia, spinal cord injuries, and other disorders. The disease when due to pernicious anemia is associated usually with the typical blood picture. Central nervous system disease is found in 80-90% of patients with pernicious anemia. In many instances (40-50%) the spinal cord lesion is already present when the anemia is discovered. In others it develops during the course of the disease. The diagnostic triad of (1) sore tongue, (2) numbness and tingling, and (3) weakness, together with macrocytic anemia and achlorhydria form a clinical picture which is well known. Failure to secrete free hydrochloric acid after maximal stimulation with histamine is so characteristic of pernicious anemia that in the absence of this finding a diagnosis of pernicious anemia must be made with much hesitation. It has been observed in some instances that achlorhydria preceded by many years the development of symptoms. The gastric secretory deficiency is usually permanent and uninfluenced by treatment.

Gastric Acid

A total of 36 to 47 cases have been described in which free hydrochloric acid was found in gastric secretion of otherwise more or less typical cases of pernicious anemia. This is not surprising, since the fundamental defect stated earlier is a failure to secrete intrinsic factor. From a practical standpoint, however, it is a good working rule to question a diagnosis of pernicious anemia if hydrochloric acid is found on gastric analysis, unless the Schilling test gives evidence of intrinsic factor deficiency.

Neuritis

Neuritis may be difficult to differentiate in the early stages with paresthesia and reflex loss, but the occurrence of nerve and muscle tenderness and the sensory findings of neuritis usually suffice as well as the absence of sphincter involvement.

Tabes

Tabes can be differentiated by the Argyll-Robertson pupils, pains, and the positive serologic test.

Multiple Sclerosis

Multiple sclerosis may be confused with the condition, but the occurrence of history of remission, temporal pallor and absence of abdominal reflexes is helpful.

Spinal Cord Tumor

Spinal cord tumor may be associated at times only with posterolateral sclerosis without evidence of superficial sensory loss. Pain is usually present. Evidence of subarachnoid block, either partial or complete, and increase of the total protein in the spinal fluid are extremely helpful in establishing tumor as a cause. Because pyramidal tract signs may predominate or may be exclusively present, primary lateral sclerosis must be considered. There is serious doubt concerning the existence of this entity, and the probabilities favor the fact that patients with pure pyramidal tract disease involving the legs or arms and legs, develop eventually other signs of nervous system disease to be diagnosed as multiple sclerosis, amyotrophic lateral sclerosis, or some other form of disease in which the pyramidal tracts are regularly affected.

Among the many other conditions which may cause a posterolateral syndrome the differentiation is not as a rule difficult, since the cause is usually clear and pernicious anemia is readily excluded by blood and gastric studies. Nutritional disorders as a cause of the syndromes must be sought in all cases with an obscure cause. Despite the most careful survey, there still remains a group of cases for which no cause seems to be found. Some of these cases prove subsequently to be due to pernicious anemia and others to multiple sclerosis; still others remain unsolved.

Treatment

The treatment is that of pernicious anemia or of whatever condition is associated with the process. The most important factor influencing the response to treatment is the duration of the disease prior to the institution of the therapy. Factors of little importance are the degree of anemia and the severity of cerebral manifestation. Larger doses of Vitamin B12 are needed for the treatment of the neurological manifestations of the deficiency than for maintenance of a normal blood-cell count. Treatment consists of the intramuscular injection of 1000 micrograms of Vitamin B12 followed by 500 micrograms twice weekly for one month. Subsequent therapy consists of the administration of 100 micrograms of Vitamin B12 by intramuscular injection once a week for the next six months. Most improvement occurs during the first 3-6 months of therapy. Relapses during therapy are usually associated with infections and can be corrected by increasing the maintenance dose of Vitamin B12.

Transfusion is now rarely required in pernicious anemia. Even when the anemia is severe the possibility of obtaining a physiologic response in 48-72 hours when specific therapy is given parenterally makes it unnecessary to subject the patient to the risks, discomfort and expense of blood transfusion.

The first sign of improvement after beginning treatment with Vitamin B12 is an increase in the number of circulating reticulocytes. This commences within 4-5 days and reaches a peak at 7-10 days; at this time they may constitute 15-40% of the total red cells. This response always heralds a general improvement and the hemoglobin concentration and red-cell counts soon begin to rise. The number of reticulocytes then falls to normal, but the hemoglobin and red-cell levels continue to rise until the normal state is restored.

Vitamin B12 is present especially in liver, kidney, muscle, yeast, milk and eggs. For therapeutic use it is produced from cultures of Streptomyces griseus, the organism which also manufactures the antibiotic Streptomycin.

Continued

Course and Prognosis

The prognosis is good with early and adequate therapy (Turner). The cause of hematological and neurological remission in pernicious anemia is unknown. A remission may last from a few weeks to 15 years. The length of time before relapse occurs in patients with pernicious anemia depends on several variables:

1. The amount of stored erythrocyte maturation factor (Vitamin B12).
2. The amount of intrinsic factor, however minute, produced by the stomach.
3. The amount of extrinsic factor(s) in the diet.
4. The occurrence of infections and degenerative disease.
5. Trauma, crushing injuries, surgery and fractures.
6. Addition of folic acid to the diet or medications in a patient with a borderline case of compensated pernicious anemia.
7. Other unknown factors.

Case Report

This 57-year-old white female, right-handed, was admitted with a two-week history of swelling, burning and numbness of the feet and a long standing anemia of at least 12 years duration. The day prior to admission she noticed tingling and numbness of the tips of the fingers. The anemia had been treated with iron preparation off and on. She had been on multivitamin tablets for two weeks. History of past illness revealed migraine headaches and cholecystectomy at age 45 for jaundice. Family history was negative. She did not smoke or drink alcohol. On system review, she was found to be tired and weak with a weight loss of about seven pounds during the preceding year. Menopause had occurred ten years before.

Physical examination revealed a well-developed, undernourished, pale, co-operative female in no acute physical distress and mentally alert. Eyes showed pale conjunctiva, no jaundice. Pupils reacted normally to light and accommodation. Eye grounds were normal. ENT examination showed smooth and pale tongue with atrophied papilla. Thyroid was not palpable. Chest was negative. Heart was regular in rate, no murmur. Abdomen was negative. Rectal and pelvic examinations were negative.

Cranial nerves were negative. There was a full range of neck motion. The arms were normal with respect to strength and sensation and co-ordination. Deep tendon reflexes were snappy and equal in the arms. The lower limbs showed no impairment of superficial sensation. There was no muscle tenderness of the calves. Impairment of heel to skin testing was noted bilaterally. There was a suggestion of impairment of great toe position sense bilaterally, but more on the right. Vibration sense was impaired at both ankles and perceived at both knees. The toe signs were equivocally positive bilaterally. A positive Romberg was noted.

Laboratory Reports

An EKG showed mild intraventricular conduction defect with nonspecific T wave changes. Upper GI series, barium enema and skull X rays were negative, Chest X rays showed evidence for generalized pulmonary emphysma and also rather prominent generalized demineralization of the osseous structures. Hemoglobin was 9.9 mg% 7,200 leukocytes, 61% polys, 29% lymphs, 6% monocytes and 4% eosinophiles. Hematocrit = 30%. Sed. rate was 85 mm. Ret. count (first) was 0.1%, platelet count 352,000. Prothrombin time, control 13.9, patient 15.9. Serum iron 53. BUN 65. FBS 92. Cholesterol 187. PBI 7.5. Creatinine 3.5 mg. Urinalysis showed a specific gravity of 1.005, trace albumin, packed WBC's. A urine culture was positive for E. coli. Stool once was 4+ for occult blood, second specimen was negative. CSF showed 27 mg% protein, 65 mg% sugar and 747 mg% chloride. No cells. Wasserman was negative. Gastric analysis revealed no free acid after a test dose of 1 mg. of Histamine. Schilling Test using Vitamin B12 Co^{60} showed 0% excretion on a 24-hour urine collection, but there was 12% excretion after giving the intrinsic factor. Bone marrow was nondiagnostic other than a normochromic anemia of peripheral blood.

Hospital Course

A diagnosis of pernicious anemia complicated by C.N.S. involvement was made and she was put on 1000 micrograms of Vitamin B12 I.M. She improved gradually with disappearance of tingling and numbness of extremities, but positive Romberg sign persisted. Vitamin B12 therapy was continued in the Outpatient Department.

M. Kohanim, M.D.

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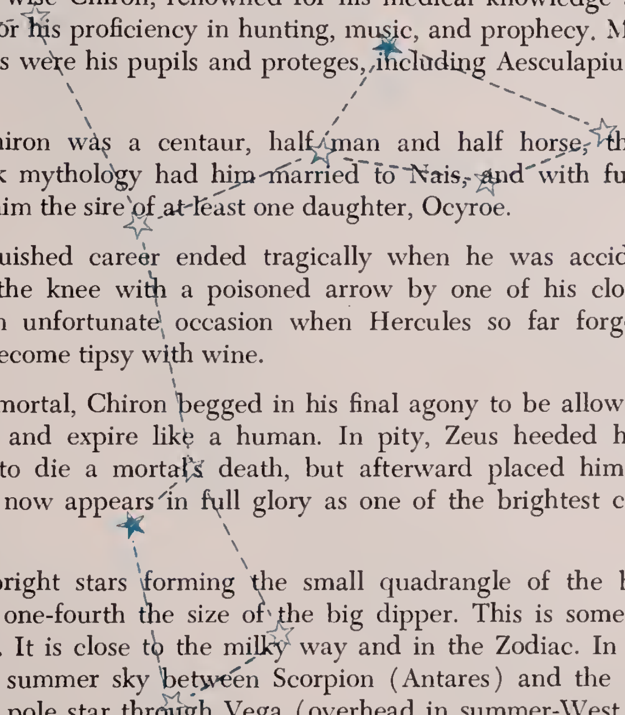
11-20 and additional information can be obtained by corresponding with — Grand Rounds Editor, Minnesota Medicine.

PHYSICIAN IN THE SKY

Chiron



One of the prominent signs of the Zodiac is Sagittarius, the Archer, representing a centaur with drawn bow. Greek mythology identifies Sagittarius with the famous and wise Chiron, renowned for his medical knowledge and surgical skill as well as for his proficiency in hunting, music, and prophecy. Many legendary Greek heroes were his pupils and proteges, including Aesculapius and Achilles.

Though Chiron was a centaur, half man and half horse, the charming license of Greek mythology had him married to Nais, and with further poetic abandon made him the sire of at least one daughter, Ocyroe.

His distinguished career ended tragically when he was accidentally and fatally shot in the knee with a poisoned arrow by one of his closest friends, Hercules, on an unfortunate occasion when Hercules so far forgot his good breeding as to become tipsy with wine.

Though immortal, Chiron begged in his final agony to be allowed to forfeit his immortality and expire like a human. In pity, Zeus heeded his plea and permitted him to die a mortal's death, but afterward placed him among the stars, where he now appears in full glory as one of the brightest constellations in the Zodiac.

The four bright stars forming the small quadrangle of the body of the archer is about one-fourth the size of the big dipper. This is sometimes called the milk dipper. It is close to the milky way and in the Zodiac. In our latitude it is low in the summer sky between Scorpion (Antares) and the goat. A line drawn from the pole star through Vega (overhead in summer-West in autumn) and projected, points directly to Sagittarius. In January, Sagittarius is below the horizon in the Northwest; we shall not see this constellation in the evening until next Spring.

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ABSTRACTS, BRIEFS AND COMMENTARIES

MANAGEMENT OF SECOND TWIN DELIVERY

The author studied 500 consecutive twin deliveries out of 20,369 total deliveries.

When twins delivered by cesarean section and macerated fetuses, which for mechanical reasons usually deliver second, were excluded, there were 38 first twins lost and 46 second twins lost. These figures were reduced to seven first and nine second twins lost when the babies were normal and weighed 2,000 grams or more. As in other studies prematurity was the major cause of fetal mortality. Only two mature twins were lost. For these reasons bed rest after the 30th week until near term is advocated. This regimen, applied to a small group of patients, reduced the deaths from prematurity from 12.5% in the whole series to 7.4%. The well-known increased incidences of pre-eclampsia, premature labor and anemia were again seen in this series.

Although there were virtually the same number of intrapartum deaths among first (9) and second (8) twins, their hazards are different. Prolapsed cord caused four deaths in 10 occurrences in the first twin but no deaths in seven times in the second twin. The second twin, however, is at a disadvantage because of malpresentation, fetal distress and potentially traumatic delivery.

The safest time interval for delivery of the second twin in this series proved to be between 10 and 20 minutes. Artificial amniotomy followed by an operative delivery under general anesthesia and amniotomy within 15 minutes after delivery of the first twin to hasten delivery produced the lowest neonatal mortality. It is therefore advocated that the membranes of the second twin be ruptured about five minutes after delivery of the first twin and the delivery completed within 20 minutes.

Franklin D. Loffer, M.D.
Minneapolis, Minn.

MacDonald, R. R.: Management of Second Twin Delivery. Brit Med J 1:518, 1962.

ADENOMA MALIGNUM OF THE CERVIX

The authors presented five case reports of adenocarcinoma of the cervix in which the primary lesion was originally interpreted as benign. Despite the benign histologic appearance, the tumor metastasized early and responded poorly to conventional therapy.

Continued

Adenoma malignum was suggested as a term to separate this highly differentiated tumor from the more commonly encountered adenocarcinoma of the cervix which responds satisfactorily to therapy. In adenoma malignum the glands are lined by a single layer of cells which are not recognizable as abnormal. This apparently normal gland cell pattern may persist to the ultimate destruction of the patient. The glands, however, are abnormal in form and arrangement and characteristically vary in size. The small glands with sharp projections apparently pushing into the surrounding connective tissue are reliable criteria for diagnosis. The authors urged that, in addition to the prompt recognition of the tumor, it be separated from the other adenocarcinomas of the cervix. This would permit the application of ultraradical surgery to this ordinarily incurable malignancy.

Leon L. Adcock, M.D.
Minneapolis, Minn.

McKelvey, J. L. and Goodlin, R. C.: Adenoma Malignum of the Cervix. A Cancer of Deceptively Innocent Histological Pattern. Cancer 16:549,1963.

THE MANAGEMENT OF HYPOFIBRINOGENEMIA IN PREGNANCY

Hemorrhage is a significant source of maternal mortality. Hypofibrinogenemia is an important source of the hemorrhage according to the authors. The article discusses a series of 18,218 obstetrical cases at Freedmans Hospital in Washington D. C. In this series are 27 cases of hypofibrinogenemia.

The authors list severe abruption with 15 noted cases as the most common cause. Ten per cent of the hospitals abruptio cases developed the disorder. Fetal death in utero (especially after the fourth week of fetal death), amniotic fluid infusion (three predisposing factors being: spontaneous or artificial membrane rupture, vigorous uterine contractions, and intravenous pitocin), and infected abortion are other lesser noted factors. During the six years covered in the survey the total maternal mortality was six, of which five deaths were attributed to hemorrhage from blood incoagulability.

In suspicious cases blood fibrinogen levels (normal is 200-600 mg%, while a hypo condition is considered at less then 150 mg%) should be obtained. Depending on the laboratory facilities and time available testing may be done by blood level, titer, fibrindex, or clotting time. Adding 40 mg. of fibrinogen to 4cc. of nonclotting blood with a resultant clot is strong evidence of a disorder.

Management of such a patient should begin with the insertion of a large bore intravenous needle. Clotting time, hemoglobin, hematocrit, type and cross match, administration of fibrinogen, and early uterine evacuation are advocated by the authors. They further state that stored bank blood is a poor way to raise blood fibrinogen level, since it contains only .75 grams per 500cc. The reported cases needed, on the average, four grams of fibrinogen to correct the deficit. Treatment must be prompt and depends on fibrinogen availability and a high suspicion index. Even the fear of high hepatitis incidence is not a deterrent to treatment.

Ernest Hopkins & John F. J. Clark. J Nat M Ass 54:464, 1962.

Lawrence J. Singher
Minneapolis, Minn.

INDUCTION OF LABOR

In cases of known intrauterine fetal abnormality or intrauterine death injection of either hypertonic saline or hypertonic glucose into the amniotic sac has been used to successfully induce labor in the first and second trimesters of pregnancy. In this study 250 cc. of amniotic fluid were drained from the amniotic cavity by transabdominal approach and were replaced with 250 cc. of 50% glucose solution. The duration of pregnancy varied from 28 to 40 weeks in the 22 patients studied. There were eight primigravidas, 16 patients with fetal death in utero and six with congenitally abnormal fetuses. Labor began from three to 85 hours after injection. Only three began labor after 48 hours. All labors were less than 13 hours in length. There were no maternal complications.

Urinary estrogen and pregnanediol levels were studied in 12 patients. The estrogen levels were low in all patients. The pregnanediol levels were low in five out of six patients in whom the fetus had died from hypoxia. There are no findings that would support changing uterine volume or uterine irritation from the glucose as a cause for the onset of labor. Although Bengtsson and Csapo's theory that labor is inhibited by a decrease in the placental production of progesterone is accepted by many, the only two patients in whom progesterone levels were studied before and after injection of hypertonic glucose did not support this theory.

Franklin D. Loffer, M.D.
Minneapolis, Minn.

Wood, C., Booth, R. T., Pinkerton, J. H. M.: Induction of Labor. Brit Med J 706, September 15, 1962.

RECURRENT JAUNDICE OF PREGNANCY

The author, in a follow-up study of 33 patients with jaundice in pregnancy seen at the Rotunda Hospital in Dublin, observed three patients in whom jaundice recurred in subsequent pregnancies. The patients all recovered completely.

The cases were presented to draw attention to the characteristic features of the disease, which is relatively unrecognized. Icterus is usually noted in the last four months of pregnancy and is preceded by pruritus. The patients are afebrile. Other symptoms, such as anorexia, are mild and inconstant. The liver is not tender and spider naevi are not present. Occasionally the signs and symptoms abate during pregnancy but more commonly they persist until one or two weeks postpartum. The serum bilirubin and alkaline phosphatase are elevated. The prothrombin time may be prolonged. Intrahepatic cholestasis is the only histologic finding and extrahepatic biliary obstruction has not been demonstrated. In one case biopsies of the liver were obtained in different pregnancies which were complicated by jaundice. The histologic appearances were identical. Recovery is complete histologically and clinically. The disease is benign for both the mother and infant.

Leon L. Adcock, M.D.
Minneapolis, Minn.

Moore, H. C.: Recurrent Jaundice of Pregnancy. A Type of Intrahepatic Cholestasis. Lancet 2:57, 1963 (No. 7298).

Continued

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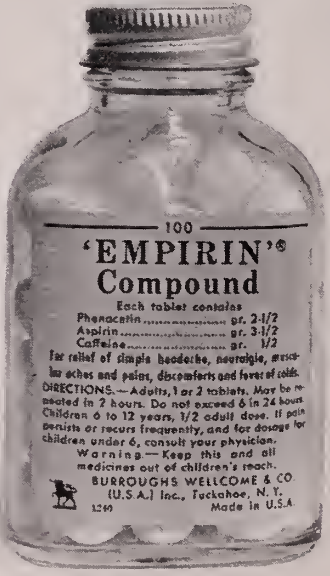
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ANESTHESIA AND MATERNAL MORTALITY

Twenty women died during pregnancy or childbirth primarily because of problems in the administration of an anesthetic agent in New South Wales during the four-year period from 1947 to 1960. Less than one half of the patients were classified as poor anesthetic risks. The deficiencies in standards of anesthesia were evenly distributed between the rural and urban areas. Frequently patients had experienced stress of labor and disturbance of physiology; in many cases toxemia, blood loss and shock from trauma had altered the general condition of the patient.

Errors in obstetric management frequently increased the risk of anesthesia. Good obstetric judgment is needed to avoid cesarean section as a last resort in management. Some factors contributing to faulty management were failure to obtain details of previous pregnancies, failure to warn the patient not to take solid food after the onset of labor, the use of a too concentrated local anesthetic solution, the administration of a slow-acting barbiturate by the intramuscular route in an emergency, failure to suspect ectopic gestation, and undue haste in operating.

Errors in the anesthetic management began in the preanesthetic period. Inadequate preparation of the patient included insufficient administration of blood, failure to aspirate the stomach of women in prolonged labor, and neglect to insure that blood was available. A wrong choice of anesthetic agent occurred when thiopentone was administered to shocked and bleeding patients. In other situations inexperienced personnel were allowed to administer the anesthetic instead of the physician using local anesthesia. A number of factors were responsible for fatalities in the period of anesthesia. Overdoses of drugs were given to patients with unstable circulation due to blood and fluid loss. Inadequate ventilation, inhalation of vomitus, technical mishaps, inadequate observation and resuscitation, and insufficient replacement of blood were other factors responsible for mortalities.

Lack of supervision in the postanesthetic period was also a fault.

Cardiac arrest occurred in 11 cases, six during cesarean section. In the majority the anesthetic agent either was used in excess or was a poor choice. Cardiac massage was properly performed in nine cases but none of the patients survived.

The physician must be aware of incompatabilities of drugs commonly used in obstetrics. Adrenalin is incompatible with chloroform, cyclopropane and halothane; pitocin is incompatible with cyclopropane and succinylcholine. Commonly used diuretics may cause sodium and potassium depletion. Cerebral and renal edema, coma and anuria can result from a subsequent water load. Chlorpromazine renders the patient extremely sensitive to other potential causes of hypotension. Atropine may lead to hyperthermia when fever is present with an enhanced tendency to convulsions. Thiopentone may partially paralyze the vasomotor center and cause profound hypotension in patients suffering from blood loss.

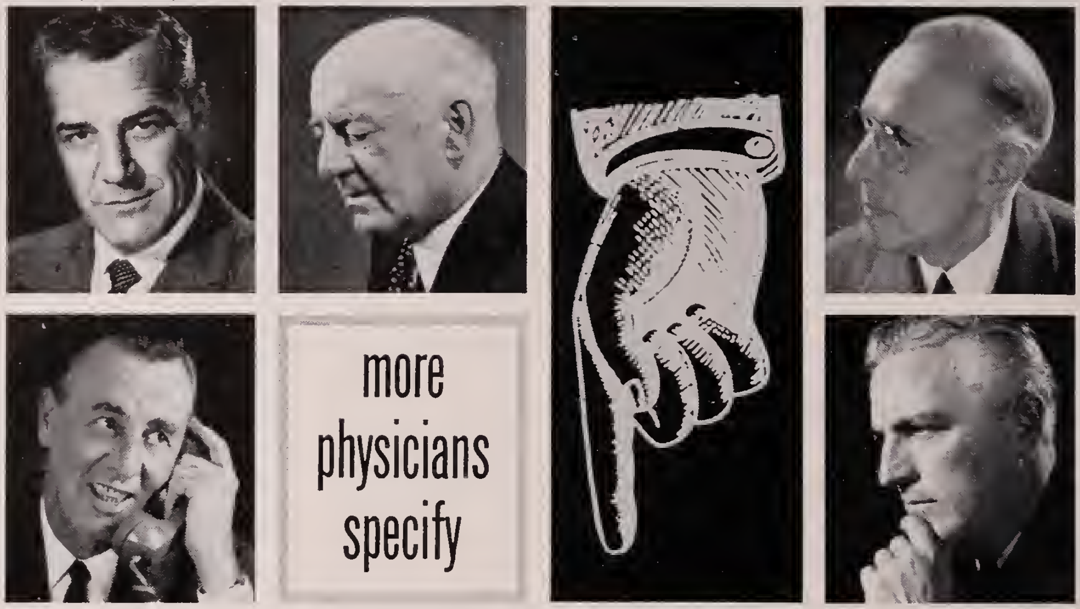
Rapid advances in methods of anesthesia and analgesia make demands that have not yet been met by an increased output of anesthesiologists.

Leon L. Adcock, M.D.
Minneapolis, Minn.

Special Committee Investigating Maternal Mortality in Deaths Under Anaesthesia in Obstetric Practice, 1957-1960. Med J Australia 2:817, 1962.

Continued

Photos posed by professional models



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ANEMIA IN RHEUMATOID ARTHRITIS

Thirty-six patients with active rheumatoid arthritis in whom anemia was slight were investigated, in part with radioiron and radiochromium, for abnormalities which might lead to anemia. The primary defect appeared to be a pronounced reduction of ability to absorb iron from the intestinal tract. An equally marked reduction in serum concentration of iron could not be attributed to the slight reduction in iron-binding capacity of the serum. Despite the reduction level of iron in the serum, the apparent turnover of iron was so rapid that the total clearance per day was normal or moderately elevated; but the fraction of the iron cleared from the blood and, appearing in the circulation in newly synthesized erythrocytes, was slightly repressed. Erythrocyte survival was normal or slightly shortened; hemolysis seemed insignificant. The fecal excretion of radioiron, which was not associated with erythrocytes, was greatly increased in two patients with no evidence of intestinal bleeding. A moderate increase in the plasma volume was a common feature.

Journal of the American Medical Association
Courtesy of References and Reviews

Roberts, F., Hagedorn, A., Slocumb, C., and Owen, C.: Blood 21:470 April 1963

CONTROL OF TUMOR IMPLANTATION DURING OPERATIONS ON COLON

In an attempt to evaluate the problem of implantation in the anastomotic site, the authors studied Brown-Pierce tumor injected into rabbits in the site of colon resection. One phase of the study involved an evaluation of the mechanical control as suggested by Cole wherein ligatures were placed at a distance from the site of anastomosis. They did not find a significant difference in tumor growth at the anastomotic site.

Chemotherapeutic studies were undertaken by employment of Clorpactin XCB irrigation. The results failed to indicate any superiority over saline in the control of implantation and was in fact even more extensive with Clorpactin than with saline. Nitrogen mustard likewise failed to effect any control.

Another study phase involved an evaluation of the value of preoperative bowel sterilization. There was no correlation between anastomotic site tumor growth and bowel bacterial flora at time of anastomosis.

When iodized suture was employed in performing the anastomosis, a highly significant difference appeared in tumor implantation at the anastomotic site. Tumor was found at the anastomosis in 21 of the 34 controls (chromic sutures), and by contrast it was present in only five of 34 animals in which iodized suture was employed, a finding of strong statistical significance.

This paper was discussed by Dr. Warren Cole, Dr. Colin Thomas, and Dr. Edward T. Krementz. All of them seem to agree that tumor recurrence at the anastomotic site is far greater than generally appreciated.

The findings of such a study naturally require confirmation by other investigators and by clinical studies in human cases to establish its value. However, this appears to be a very well designed study; and since it is a new approach it may well represent another milestone in the slow but definite progress in the control or management of cancer.

J. H. Strickler, M.D.
Minneapolis, Minn.

Isadore Cohen, Jr., M.D., C. Edward Floyd, M.D., M. Atik, M.D.: Ann Surg 157:825 June 1963

Continued

INTRAVASCULAR PRESSURE, VASCULAR TONE, AND SYMPATHECTOMY

The author briefly reviews the history of sympathectomy and the response of the vascular tree in the laboratory and clinical sphere.

He concludes that sympathectomy improves circulation only if dilatable arterioles are present. There is, however, an early and late response of the blood vessel to sympathetic denervation which may invalidate results of the procedure.

Early (days to weeks) — subsidence of vasodilation results from (a) development of intrinsic tone in the arteriolar smooth muscle in response to increased stretch and lateral pressure, (b) secondary medial hypertrophy of the artery wall because of this, and (c) incomplete denervation of the sympathetic fibers because of various anatomical variations and regenerative phenomena. The author presents evidence that the *completely* denervated arteriole (or any other effector organ as muscle, sweat gland, etc.) is *not* unusually sensitive to circulating humeral agents (epinephrine) and therefore discounts this factor as a cause for the early occurrence of vasoconstriction.

Late (months to years) — return of arterial insufficiency after sympathectomy results from two causes: first, the "natural course" of the arteriosclerotic disease, and second, the regeneration of severed sympathetic fibers with anastomosis to the severed fibers. This rarely occurs after five years.

Sympathetic denervation therefore initially results in arteriolar dilation and decrease in resistance. If *incomplete* in time, 30% to 50% of the cases of postganglionic nervous activity may become indistinguishable from the preoperative state (sensitization of the *partially* denervated neurons or reinnervation by twigs from intact neurons.

Complete denervation of the lower extremity is anatomically more possible than of the upper extremity. Lumbar sympathectomy should include the chain between the first and fifth ganglia (impotence a factor in men). The inferior and middle cervical ganglia and the upper four thoracic ganglia must be removed to obtain (or nearly so) denervation of the upper extremity.

This is an excellent bibliography and succint summary of a vast field important to the surgical and nonsurgical physician in the care of patients with vasospastic or arteriosclerotic vascular insufficiency.

Jerome T. Grismer, M.D.
Minneapolis, Minn.

F. A. Simeone, M.D.: Surgery 53, 1, 1963

TREATMENT OF STOMAL ULCER

Twenty-five cases of stomal ulceration were treated by total transabdominal vagal resection with cure in all and no operative mortality. The stomal ulcer rate in over 900 cases of duodenal ulceration treated by vagal resection and gastroenterostomy was under 0.5% and occurred only when vagal section was incomplete. Complete vagal resection is the operation of choice for stomal ulceration. Complete vagal resection with gastro-enterostomy or pylorplasty is advocated as the best treatment for duodenal ulceration.

Courtesy of References and Reviews
Journal of the American Medical Association

MacKelvie, A.: Lancet 1:1073, May 18, 1963

Man knows his age; woman computes hers.

BOOK REVIEWS

SYNOPSIS OF OPHTHALMOLOGY Second Edition — William A. Havener M.D., C. V. Mosby Company, 1963. 395 pages, glossary, index, numerous black and white photographs and illustrations, no references. Price $7.85.

The original 1959 Synopsis has been brought up to date by the author, Professor of Ophthalmology at Ohio State University. This book has been written not as a concise text for the medical student or ophthalmology resident but as a reference work for the general practitioner or specialist who may encounter eye problems. The author shows great interest in the education of non-specialists in the preventive aspects of eye care. He states in the preface, "Seemingly trivial details may make the difference between a well-treated, seeing eye and visual tragedy."

Differential diagnosis of serious and self-limited problems is stressed with short case histories. The difficult problem of diagnosing glaucoma, present in 2% of our adult population, is discussed. Principles of first aid and simple office procedures such as probing the lacrimal duct are outlined. There is a section to help one understand the various types of eye surgery. The indiscriminate use of steroid containing eye drops which may turn a simple herpes infection into a blind eye is condemned.

To my knowledge, this is the best book available for this purpose. It is written in simple language, modern, well-organized and copiously illustrated. Every physician would benefit by having reference to this volume.

William S. McClanahan, M.D.
Minneapolis, Minn.

MEDICAL MYCOLOGY — Emmons, Binford, and Utz. Lea & Febiger, Philadelphia, 1963. 380 pages, $14.00.

This commendable book represents a very well illustrated presentation of the mycoses. The initial chapters, broad in scope, acquaint the reader with some of the terminology, classification, and more general relations of the fungi to the field of medicine. The discussion of the individual mycoses that follows, provides thorough clinical and epidemiological descriptions, histopathologic descriptions and procedures, methods of laboratory diagnosis and therapeutic approach. There are excellent gross and microscopical photographs of each of the mycoses. The three appendices to the text describe methods of collection and examination of specimens and contain detailed information for the preparation of culture media and various staining techniques.

"Medical Mycology" will be a useful book for the internist, general practitioner, dermatologist and pathologist. The laboratory bacteriologist will also find it helpful. The lack of descriptions and comparisons of the common culture contaminants is a slight drawback.

Calvin Bandt, M.D.
Minneapolis, Minnesota

Greatness

It is force of principle which measures moral greatness — that highest of human endowments, the brightest manifestation of the Divinity. The greatest man is he who chooses the right with invincible resolution, who resists the sorest temptations from within and without, who bears the heaviest burdens cheerfully, who is calmest in storms, and most fearless under menace and frowns, whose reliance on truth, on virtue, is most unfaltering.

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Minneapolis, Minn.

Blood Bank Procedures

Evaluation of Training Program in Hospitals in Minnesota*

"Technics" of blood banking become more exacting with increasing knowledge of immunohematology. Competence of laboratory personnel in this field is essential. This statewide survey is of vital interest to all physicians.

This evaluation study points out a serious time lag between the recognition of new developments in blood-bank procedures and their use in the field. This study was initiated in 1958 as part of the existing Minnesota Civil Defense and Disaster Blood Program.[1,2] Special training was offered to increase the number of laboratories performing blood-bank procedures and to increase the use of more complete grouping, typing, and cross-matching procedure. In 12 separate surveys from October 1958 through September 1961 a total of 45 specimens was distributed. ABO grouping and $Rh_0(D)$ typing were requested on all specimens; cross-matching results were requested only during the last half of the study.

The data on accuracy of reported results are presented here according to group and type of specimen, hospital size (number of beds), attendance of personnel at special training courses, the use of various technics, and the groups of individuals signing the reports.

Materials and Methods

The co-operation of the following interested state organizations was obtained prior to the initiation of the study: Minnesota State Medical Association, Minnesota Society of Clinical Pathologists, Minnesota Society of Medical Technologists, and Minnesota Hospital Association. Assistance, particularly in planning the study, was given by a technical advisory committee including representatives from several of these organizations.

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*From the Minnesota Department of Health with the cooperation of the Minnesota Department of Civil Defense.

**Chief, Section of Special Laboratory Studies, Division of Medical Laboratories, Minnesota Department of Health.

†Deputy Executive Officer and Director, Division of Medical Laboratories, Minnesota Department of Health.

§Medical Laboratory Consultant, Minnesota Department of Health, present address: Badger Regional Blood Center, Madison, Wis.

Continued

The study was financed by state and federal funds available for the Minnesota Civil Defense and Disaster Blood Program.[1,2]

A survey of blood banks in Illinois had been reported by McDaniels.[3] This report and consultation with its author provided guidance in planning the Minnesota program.

Four laboratories were invited to serve as reference laboratories and all accepted. Results from reference laboratories are excluded from the presentation.

Participants

Licensed general and specialized hospitals in Minnesota were invited to participate. Letters announcing the program were sent to hospital administrators, pathologists and chief technologists. As new hospitals opened they also were invited to join the program. The invitational letter pointed out the value of this state-wide comparison of results and stated that identification would be by code number only. During the entire study period there was a total of 200 possible participants. A few laboratories initially declined to participate; during the study others asked to be excluded. At intervals laboratories from which reports were not received were asked if they wished to continue in the study and the expressed wish was followed. Laboratories which did not reply to these inquiries were dropped from the list after failure to report on two consecutive surveys.

Specimens

Blood specimens were purchased from one of the reference laboratories as citrated whole blood (480 ml. of whole blood in 120 ml. of acid citrate dextrose solution). The directors and laboratory personnel of the reference laboratories agreed that the plasma would be satisfactory for reverse typing. Blood samples from three or four donors were distributed in each of the 12 surveys, a total of 45 specimens. To control bacterial contamination, 100 units of penicillin and 100 micrograms of streptomycin per milliliter were added to each donor bottle. Each specimen consisted of a 3.0 ml. volume dispensed into a numbered, two-dram flat-bottomed vial (Kimble 60900) which had been corked prior to sterilization (dry heat 175° C. for two hours).

Antisera for use in ABO grouping and $Rh_o(D)$ typing were not supplied to participants for use in the survey. Variation in the antisera used by participants was pertinent in regard to $\mathfrak{R}h_o(D^u)$ specimens, since some anti-$Rh_o(D)$ serum will give a positive reaction to some $\mathfrak{R}h_o(D^u)$ specimens. A strict interpretation of results was used; a negative $Rh_o(D)$ report was required on an $\mathfrak{R}h_o(D^u)$ positive specimen.

In June 1960, the study was expanded to include cross matching. Serum from one donor and citrated cells from another donor of the same blood group and $Rh_o(D)$ type were used. The serum was dispensed in the usual manner and the vial was labelled "patient serum." The citrated cells were dispensed in vials labelled "patient cells." The two or three other specimens distributed for grouping and $Rh_o(D)$ typing in the same survey were the potential donors; these were identified by number. The potential patients selected were not incompatible with potential donors, due to isoagglutinins. Since serum was not available from immunized patients, it was necessary to add the desired antibody from a commercial source to the serum. Slide test antibody was used, in which incomplete antibodies predominated, but complete antibodies had not been eliminated. The use of the indirect Coombs test was not necessary to detect the antibodies in these artificially immunized patients. The "patient serum" used for the survey in March 1961 turned out to contain too little antibody, a fact confirmed by the results from reference laboratories and from participants. This survey was therefore eliminated from the evaluation of cross-match results.

Specimen Numbering

Since there were less than 200 participants, the numbers 1-200 were assigned to the first donor, numbers 201-400 to the second donor, 401-600 to the third donor, etc.

Specimen Transportation

Specimens were mailed in the afternoon via parcel post and were delivered to reference laboratories and almost all participating hospitals the next morning. A form enclosed with each shipment of specimens provided for reporting the date and condition of specimens upon receipt, the ABO and $Rh_o(D)$ typing results, the use of reverse (serum antibody) typing, and the signature of the person making the report. During the last six surveys an additional report form was included, requesting saline, albumin, and indirect Coombs test cross-match results.

Reports to Participants

A report of all of the findings, identifying participants and reference laboratories by code number only, was mailed to each participating hospital after each survey. These reports were prepared after the expiration date (21 days) for the blood specimens.

Training Procedures

Special training in blood-bank procedures was of three types: *continuous, central,* and *regional.* One large central blood bank has the policy of requiring all affiliated hospitals to send a laboratory representative to its training laboratory for one week each year. This *continuous* program has been maintained for over five years and the curriculum has been published.[4] This training had been supplemented by a procedure in which the central bank checks the grouping and typing performed by affiliates on blood (less than 10 days old) which had been collected and sent to the central bank for credit.

Central

This large central bank agreed to accept representatives from nonaffiliated hospitals for the one week's training course in blood bank procedures that is offered to affiliates. Half of the tuition for these additional students was paid with monies available for the civil defense program and half by the participating hospital. This central training was begun in June 1958, prior to distribution of unknown specimens, and continued during the first six surveys. A comparison of results before and after training has not been made, because too few results were reported by these hospitals before their representatives received this central training.

Regional

During the study regional training courses were organized in five areas of Minnesota, because comparatively few participating hospitals sent representatives to the central training courses. Medical Technologists (American Society of Clinical Pathologists) with extensive experience in blood-bank procedures were hired as instructors for regional training courses, each course including 24 hours of instruction. Some regional courses were given evenings during several weeks; others were completed in three consecutive days.

Technical recommendations covered in the curriculum for these courses and pertinent to this report were: 1) direct and reverse (serum antibody) typing, 2) use of anti-$Rh_o(D)$ serum if only one Rh antiserum was used, 3) use of three cross-match technics (saline, albumin, and indirect Coombs test) with emphasis on the limitations of the saline cross match if used as the only cross-matching technic.

The Student Personnel

Students attending these courses varied widely in basic education and laboratory experience. Some were college graduates in medical technology and were registered as Medical Technologists (ASCP); others had had various shorter periods of formal instruction in laboratory work or on-the-job training.

Profession or occupation of the individuals signing reports have been separated into two major groups for correlation with reported results: 1) Medical technologists registered by the Board of Registry of Medical Technologists of the American Society of Clinical Pathologists; and 2) all other laboratorians. A few report forms were either unsigned or were signed by licensed physicians registered with the Minnesota State Board of Medical Examiners or hospital administrators as shown on the application for hospital license. These have been eliminated because each group was small (3% or less of total results), and also because the signature of a physician or hospital administrator may indicate either the person actually performing the blood-bank procedures or taking administrative responsibility for the laboratory work.

The signatures of individuals classified in groups 1 and 2 were in most instances known to be those of the individuals actually performing the tests reported. Group 2 was the largest and included three college graduates in medical technology who were not registered Medical Technologists (ASCP), three college graduates in other specialties, nine Medical Laboratory Assistants, registered by the Minnesota Society of Clinical Pathologists and the Minnesota Society of Medical Technologists, numerous graduates of commercial schools, many individuals

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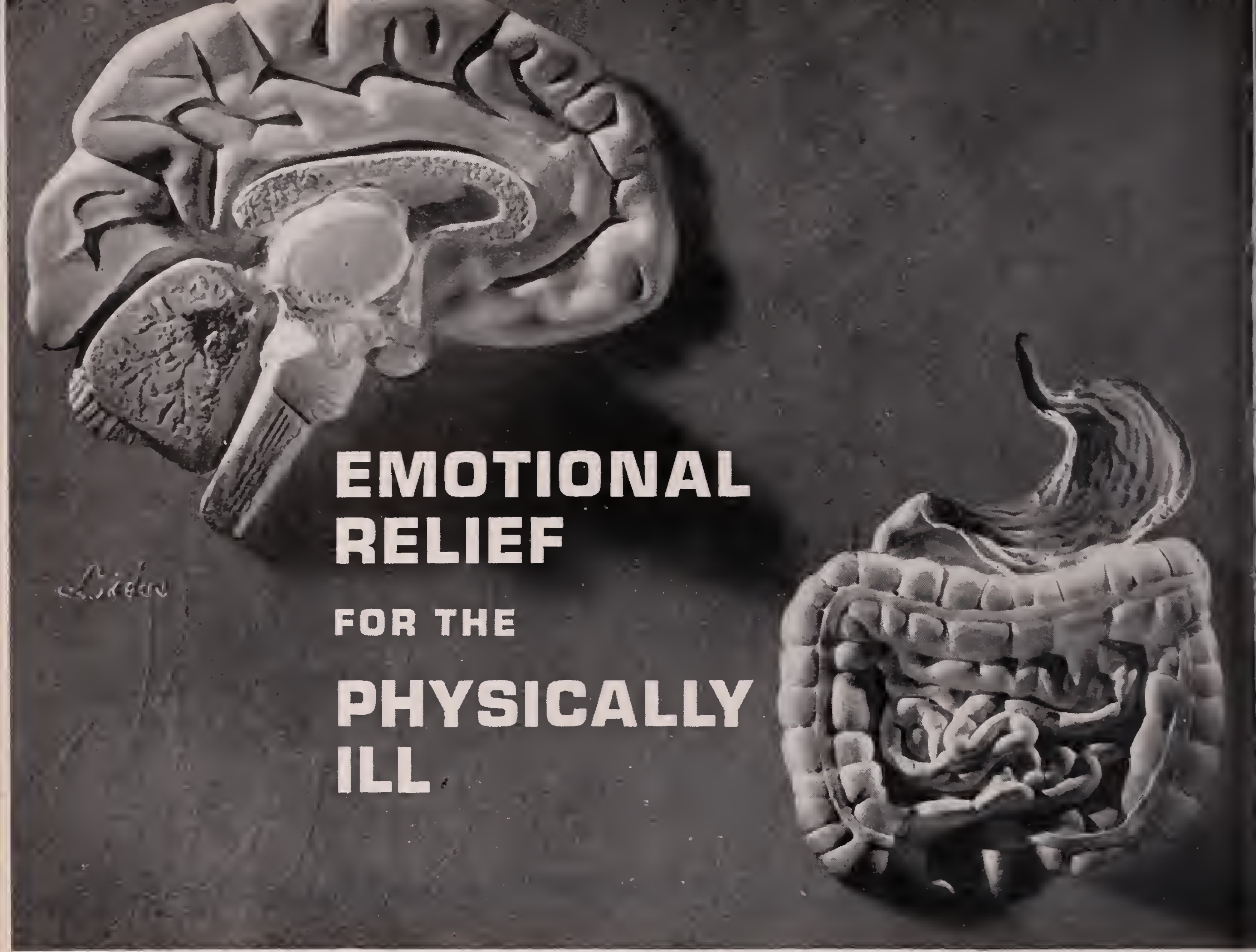

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with on-the-job training, and many for whom training was not reported. The technologists (group 1) on the average have had more intensive basic education in clinical laboratory procedures than the individuals in group 2.

On a small proportion of the reports signatures of two or more individuals appeared. For correlation of reported test results with the appropriate profession or occupation group the following priorities were selected: if any signer was a Medical Technologist (ASCP) the results were so credited; if a physician or administrator cosigned with a laboratorian, the results were credited to the laboratorian.

In the presentation of results, differences in the percentage of incorrect results in blood-bank procedures are considered to be significant only if the difference could have occurred by chance less than five times out of 100.

Results

ABO Grouping, Rh$_0$(D) Typing

The number of laboratories to which specimens were mailed decreased from 190 in the first survey to 120 in the last. The number of participants reporting results declined progressively from 170 and 174 on the first two surveys to 114 and 113 on the last two. The percentage of reports received from laboratories to which specimens had been mailed varied from 85 to 96 per cent, except for surveys 7, 8 and 9, when 78 to 80 per cent of reports were received. These three surveys were the first ones on which cross-matching results were requested.

A total of 45 specimens were distributed in sets of three or four specimens in each of the 12 surveys. During the entire study a total of 185 laboratories reported results on from four to all 45 specimens. Totals of 6468 ABO grouping results and 6457 Rh$_0$(D) typings were reported.

All ABO groupings were correct in four of the 12 surveys. On individual specimens there was a variation of no incorrect results on 25 specimens to 10 incorrect results on one specimen. Incorrect results in Rh$_0$(D) typing on each survey varied from one to 102 and on individual specimens from none on five specimens up to 93 on one specimen.

There were 58 (0.9 per cent) errors in ABO grouping in the 6468 reported results (see Table 1). The distribution of incorrect results was not random among the various ABO groups. Incorrect results on the 19 group O specimens were significantly less frequent, only four (0.1 per cent) in the total of 2681 results. Incorrect results were significantly more frequent in specimens that contained subgroups of A_*† (Not A_1): nine (5.6 per cent) errors in 160 results on one A_* and 22 (5.7 per cent) errors in 387 results on three A_*B specimens. For the remaining 22 specimens in other ABO groups, the frequency of incorrect results did not vary significantly among these groups nor from the incorrect results on the entire 45 specimens.

TABLE I
Incorrect Results in ABO Grouping as Associated with the Blood Group

Group	Specimens No.	Reported Results No.	Incorrect Results No.	%
A	10	1403	7	0.5
A_*†	1	160	9	5.6
B	5	770	8	1.0
AB	7	1067	8	0.7
A_*B	3	387	22	5.7
O	19	2681	4	0.1
Total All Groups	45	6468	58	0.9

A_*† = Subgroup of A (not A_1); subgroup A_2, A_3 or A_4 was not established.

There were 246 (3.8 per cent) incorrect results in Rh$_0$(D) typing, and these also were not randomly distributed among the Rh$_0$(D) types (see Table 2). The 1.5 per cent of incorrect results on Rh$_0$(D) positive specimens was the lowest. Accuracy of reported results on Rh$_0$(D) negative specimens varied significantly with the presence or absence of the $\Re h_0(D^u)$ variant; 2.3% of the results were incorrect if this variant was absent, 6.7% were incorrect on five specimens in which this variant was present, and 58.1% were incorrect on one specimen, No. 9, which was a high grade $\Re h_0(D^u)$.

The donor of specimen No. 9 had been tested previously, but the unusually strong reaction had not been noted. On the basis of the experience of the reference laboratories the high percentage of errors was expected. This specimen has been eliminated from the evaluation of Rh$_0$(D) results (see footnote Table 2) because the correct result was more dependent on the antisera used than on the correct performance and interpretation of the typing.

Continued

TABLE 2
Incorrect Results on Rh$_0$(D) Typing as Associated with Rh Type

Rh Type		No. of Specimens	No. of Reported Results	Incorrect Results	
Rh$_0$(D)	$\mathfrak{R}h_0(D^u)$			No.	%
Positive		19	2702	41	1.5
Negative	Negative	20	2938	68	2.3
Negative	Positive	5	657	44	6.7
Sub Total		44	6297	153	2.4
[Negative	Positive	1	160	93	58.1]*
Total		45	6457	246	3.8

*One high grade $\mathfrak{R}h_0(D^u)$ specimen, No. 9, was eliminated from the study for purposes of evaluating accuracy of results reported by individuals and by each laboratory.

On Table 3 the 154 laboratories from which 21 to 45 specimen results were available are shown categorized as to the accuracy of results as associated with hospital size (number of beds). All results from 80 laboratories were correct. All ABO results were correct, but one or more Rh$_0$(D) results were reported incorrectly by 40 laboratories. Accordingly, a total of 120 laboratories reported all ABO groupings correctly. Sixteen laboratories reported incorrect results on ABO groupings only, and 18 reported incorrect results on both ABO grouping and Rh$_0$(D) typings. In general, the accuracy of test results was highest from the largest hospitals; conversely, the smallest hospitals reported more incorrect results, particulary in ABO groupings.

An additional 31 participants reported results on only four to 20 specimens, and 15 hospital laboratories did not participate in the study. These 46 hospitals, which participated less actively or not at all included 26 small or specialized hospitals, 15 with 21 to 70 beds, and five with 71 or more beds. Thus participation as well as accuracy of test results was associated with hospital size.

The superior performance from large hospitals (over 100 beds) in two metropolitan areas (Minneapolis-St. Paul and Duluth) was noteworthy. All 23 of these large metropolitan hospitals participated actively and all results were reported correctly from 20 (87 per cent). Only two ABO and three Rh$_0$(D) results were incorrect.

Among the 154 actively participating laboratories, continuous training in blood-bank procedures had been available to 39, and representatives from 17 of these 39 laboratories also attended the central or regional training courses. Continuous training was not available to representatives from 115 of the actively participating laboratories; 20 sent representatives to the central training courses, 22 sent representatives to the regional training courses, and 73 sent no representatives to either of the courses.

Table 4 shows the association of incorrect results with the three types of training. Laboratories to which continuous training had been available showed the best record; laboratories represented at none of the training courses showed the poorest record. Performance by laboratories represented at central and regional training courses was intermediate between these two.

The influence of special training is better measured by comparing results before and after the training. Table 5 summarizes the errors reported from 28 hospitals both before and after regional training. There was no significant difference in the percentage of ABO or Rh$_0$(D) errors before and after regional training. The individual who attended the course did not sign all reports from his laboratory. Tabulations are also presented to show only the results for which the student had signed the report (see Table 5). A slightly lower percentage of errors (not significant) was reported after the regional training course than before. It is noteworthy that the percentages of ABO and Rh$_0$(D) errors both before and after the regional training course were lower than the 0.9 per cent ABO errors and 2.4 per cent Rh$_0$(D) errors reported by the entire group of participants.

The use of reverse typing was encouraged in training courses. During the early surveys about 28 per cent of the laboratories reported the use of reverse typing. In later surveys this increased to about 40 per cent, but there was no increase in the number of laboratories using reverse typing. In general, the laboratories doing reverse typing were the ones which also continued to participate during the three-year study.

Cross Matching

Cross-matching results from five surveys are presented in Table 6. In three of the five surveys antibody [anti-Rh$_0$ (D) or anti-hr′(c)] was added to the potential "patient serum." These five surveys provided a total of five incompatible and eight compatible donors.

TABLE 3
Hospital Size (Number of Beds) as Associated with Four Categories of Correctness of Results on ABO Grouping and Rh_0 (D) Typing

			Hospital Size					
			Small		Medium		Large	
Categories of Correctness of Results	Total Laboratories		0-20 beds*		21-70 beds		71 or more beds	
	No.	%	No.	%	No.	%	No.	%
All results correct	80	51.9	13	38.2	36	48.0	31	68.9
ABO results correct One or more Rh_0(D) results incorrect	40	26.0	6	17.6	25	33.3	9	20.0
One or more ABO results incorrect Rh_0(D) results correct	16	10.4	6	17.6	6	8.0	4	8.9
One or more results incorrect on both ABO and Rh_0(D)	18	11.7	9	26.5	8	10.7	1	2.2
Total	154**	100.0	34*	100.0	75	100.0	45	100.0

*Includes laboratories associated with specialized hospitals giving long-term patient care (mental, tuberculosis and other) for which the number of beds does not correlate with clinical laboratory activity.
**Includes the actively participating laboratories; reports received on 21 to 45 specimens.

Table 4
Four Categories of Correctness of ABO Grouping and Rh_0(D) Typing Results as Associated with Special Training Given to Representatives from Actively Participating Hospital Laboratories*

		Known Recent Training in Blood Bank Procedures**						No representation at Training Courses	
		Continuous		Central		Regional			
Categories of Correctness of Results	Total No. Laboratories*	No.	%	No.	%	No.	%	No.	%
All results correct	80	26	66.7	11	55.0	11	50.0	32	43.8
ABO results correct, One or more Rh_0(D) results incorrect	40	9	23.1	5	25.0	8	36.4	18	24.7
One or more ABO results incorrect, Rh_0(D) results correct	16	3	7.7	2	10.0	—	0.0	11	15.1
One or more results incorrect in both ABO and Rh_0(D)	18	1	2.5	2	10.0	3	13.6	12	16.4
TOTAL	154*	39†	100.0	20	100.0	22	100.0	73	100.0

*Including laboratories reporting results on 21 to 45 specimens.
**Continuous = Affiliated with blood bank which annually gives training in blood bank procedures to a laboratory representative from each affiliated hospital.
**Central = One or more individuals attended central training courses.
**Regional = One or more individuals attended regional training courses.
†Representatives from 17 of the 39 laboratories also attended central or regional training courses.

Continued

On Table 6 the number of reports and the percentage of incorrect results by each of three technics (saline, albumin, and indirect Coombs test) are included for compatible and incompatible cross matchings. The saline technic was reported by the largest number of laboratories and included the lowest percentage (2.8 per cent) of errors on compatible donors and the highest percentage (90.5 per cent) on incompatible donors. The indirect Coombs test was reported by the fewest laboratories and contributed the largest percentage of errors (6.3 per cent) on compatible donors and the lowest percentage (17.4 per cent) on incompatible donors. The albumin test was intermediate in use and percentage of errors. When considering any and all of the three technics there were 908 reports on the eight compatible cross matchings, with 68 (7.5 per cent) incorrect results, and 579 reports on the five incompatible cross matchings, with 135 (23.3 per cent) incorrect results.

During the study there was no increase in accuracy of results on compatible donors, but considerable improvement in accuracy on incompatible donors was observed. Compatible donors were included in four of the five surveys, and incorrect results varied from 6.9 per cent on the first, 6.6 per cent on the second, 4.9 per cent on the third and 11.0 per cent on the last survey. Incompatible donors were included in three of the five surveys, and incorrect rsults varied from 31.7 per cent on the first, 24.0 per cent, and 13.5 per cent on the last survey in which incompatible donors were included.

The saline technic would seldom detect anti-Rh antibodies as used in this survey. The 90.5 per cent errors with the saline test are in all probability not errors in test performance or interpretation of test results, but incorrect results due to the inadequacy of the technic. An incorrect result with the saline technic was counted as an error in the "over-all" cross-matching results only when the antibody in the "patient serum" was not detected by another technic.

Among the total 200 potential, participating hospitals, 45 did not take part in the cross-matching survey. An additional 58 laboratories reported results on only two to nine of the 13 tests; this limited participation was considered inadequate for evaluating accuracy of test performance. These 103 hospitals included 46 small, 46 medium, and 11 large hospitals.* In Table 7 the 97 actively participating laboratories (reporting results on 10 to 13 specimens) are shown according to hospital size in four categories: 32 reported all results correctly; 16, incorrect results on compatible tests only; 33, incorrect results on incompatible cross matches only; and 16, incorrect results on both types of cross match. Large hospitals more frequently reported all results correctly; conversely, few small hospitals reported all results correctly.

Performance on cross matching as associated with training followed a similar pattern to that observed for ABO grouping and $Rh_o(D)$ typing. The best performance was associated with continuous training (59% reported all results correctly). The poorest performance was associated with hospitals represented at none of the training courses (17% reported all results correctly). Performance from laboratories represented at central and regional courses was intermediate, with about one third reporting all results correctly. Half of the laboratories from which no representatives attended special training courses reported incorrect results on the incompatible cross matching only. The fact that a substantial number of these laboratories used only the saline technic during all or the major portion of the five surveys accounted for this high proportion of incorrect results.

All special training courses emphasized the limitations of a saline cross-match test and encouraged the use of three technics (saline, albumin, and indirect Coombs test). Table 8 shows the number and percentage of laboratories reporting one, two or all three technics during the five surveys. The decrease in the number and the percentage of laboratories reporting the results of the saline test only during the five surveys was substantial. Also, the increase in the number and percentage of laboratories using all three technics during the five surveys was substantial.

Examination Grades

At the regional training courses identical examinations were given to students at the beginning and end of the courses. Each examination included three parts: donor selection, blood collection and storage (30 questions); ABO grouping and Rh typing (20 questions); and cross-matching procedures and the rare blood

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*Hospital size (number of beds) defined in Table 3.

TABLE 5
Comparison of Accuracy of Results on ABO Grouping and $Rh_0(D)$ Typing Reported Before and After Regional Training Courses

	Before Regional Training					After Regional Training				
	Total Results Reported	Incorrect Results				Total Results Reported	Incorrect Results			
		ABO		$Rh_0(D)$			ABO		$Rh_0(D)$	
	No.	No.	%	No.	%	No.	No.	%	No.	%
28 Hospital Laboratories Represented*	471	3	0.6	6	1.3	583	3	0.5	10	1.7
30 Individuals signing reports	392	3	0.8	8	2.0	457	1	0.2	5	1.1

*Representatives from 29 hospitals attended regional training courses and reported results on 21 to 45 specimens; one hospital was eliminated because no reports were received prior to the regional training course.

TABLE 6
Percentage of Incorrect Results by Three Technics and "Over-All" Cross-Matching Results on Compatible and Incompatible Donors

		Technic Used						"Over-All" Cross-Matching Results		
		Saline		Albumin		Indirect Coombs Test		Total*	Incorrect	
Donor Group	No. of Donor	No. Results	Incorrect %	No. Results	Incorrect %	No. Results	Incorrect %	No. Results	No.	%
Compatible	8	779	2.8	748	4.0	701	6.3	908	68**	7.5
Incompatible†	5	495	90.5	453	30.2	437	17.4	579	135‡	23.3

*Total "over-all" results include the number of specimens reported by all laboratories regardless of the number of technics used on each specimen.

**Incorrect "over-all" results on compatible donors include incompatible results on each specimen whether obtained by one, two or all three technics.

†Incompatible donors were not incompatible due to isoagglutinins but due to anti-$Rh_0(D)$ or anti-hr'(c) antibody in the "patient serum."

‡Incorrect "over-all" results on incompatible donors include only specimens reported as compatible by all technics used on the specimens.

TABLE 7
Categories of Incorrect Results on Cross Matchings from 96 Actively Participating Hospital Laboratories* as Associated with Hospital Size (Number of Beds)

Incorrect results in Cross Matching	Laboratories		Hospital Size					
			Small 0-20 beds**		Medium 21-70 beds		Large 71 or more beds	
	No.	%	No.	%	No.	%	No.	%
None	32	33.3	2	13.3	12	27.9	18	46.2
On Compatible only	16	16.7	2	13.3	6	14.0	8	20.5
On Incompatible only	33	34.4	7	46.7	16	37.2	10	25.6
On Both Compatible and Incompatible	16	15.6	4	26.7	9	20.9	3	7.7
TOTALS	97*	100.0	15	100.0	43	100.0	39	100.0

*Results reported on 10 or more of the 13 cross matchings.

**Includes laboratories associated with specialized hospitals giving long-term patient care (mental, tuberculosis and other) for which the number of beds does not correlate with clinical laboratory activity.

Continued

groups (20 questions). All three parts of both examinations were given to 41 of the 50 students attending the courses. The average percentile grade was 57 per cent before and 73 per cent after the courses. Among the five regional courses, improvement in the average grade varied from 10 to 20 per cent.

Signing Reports

Signatures were requested on all report forms and were almost always included. In the entire survey the signatures of 491 individuals appeared at least once. All 18 reports received from a few laboratories were signed by the same individual. The 491 individuals included 12 licensed physicians, nine hospital administrators, 153 registered Medical Technologists, and 317 other individuals with varying amounts of known formal or on-the-job training, and some for whom the type and amount of basic education were not reported.

Table 9 shows the total number of results reported and the incorrect results in ABO grouping, $Rh_o(D)$ typing, and both compatible and incompatible cross-matching tests as associated with the two professional or occupational groups of individuals signing reports.

Medical Technologists signed reports for 35 to 39 per cent of results on the four types of procedures. The percentages of incorrect results on all four procedures were lower than those for the total survey: 0.3 per cent on ABO groupings, 1.2 per cent on $Rh_o(D)$ typings, 6.5 per cent on compatible cross matchings, and 8.2 per cent on incompatible cross matchings. Since the most serious incorrect result in these blood-bank procedures is one in ABO grouping, it is worth noting that the eight incorrect ABO results were reported by only three of the 153 Medical Technologists who signed reports.

The 317 individuals with various types of training signed reports on slightly less than 60 per cent of the results on the four types of procedures. The percentages of incorrect results on all four procedures were higher than those for the entire group: 1.1 per cent on ABO grouping, 3.0 per cent on $Rh_o(D)$ typings, 8.5 per cent on compatible cross matchings, and 32.9 per cent on incompatible cross matchings.

The difference between the percentages of incorrect results reported by Medical Technologists and by the group of individuals with heterogeneous types of training has been analyzed for significance. The difference in incorrect results on ABO groupings is significant ($P = < .01$); the difference in the $Rh_o(D)$ errors is also significant ($P = < .001$). The smallest difference was observed in the errors on compatible cross matching: 6.5 per cent for Medical Technologists and 8.5 per cent for the heterogeneously trained group; this difference was not significant ($P = < .50$). The incorrect results on incompatible cross matchings were 8.2 per cent and 32.9 per cent, a significant difference ($P = < .001$).

Discussion

The percentage of errors was low on ABO grouping (0.9 per cent), but these must be classified as the most serious errors made in the study because of the possibility of fatal consequences. The errors were lowest in group O specimens and highest in those containing A subgroup antigens other than A_1. Weaker agglutination, which is characteristic of these subgroups, probably contributed to the errors. Discussion of actual details of testing procedures with students in training courses has suggested a further possibility. In some laboratories the ABO grouping and $Rh_o(D)$ typing were performed on the same slide. When the slide was warmed for the Rh test, the disappearance of agglutination in the anti-A serum of the grouping test may have been misinterpreted.

Incorrect results on several reports suggested clerical errors. For example, in four surveys including both a group A and a group B, there were 14 errors. The majority of these were reported in pairs from the same laboratories: the A specimen reported as a B and the B as an A. These, as well as others, might well be due to clerical errors or misinterpretation of the results.

The 3.8 per cent incorrect results on $Rh_o(D)$ typing was also low, and even lower (2.4%) when the difficult specimen, No. 9, high grade $\mathfrak{R}h_o(D^u)$, was eliminated.

The percentages of incorrect results on compatible cross matchings (7.5 per cent) and incompatible cross matchings (23.3 per cent) were both surprisingly high. The increasing use of albumin and indirect Coombs technics during the study had opposing effects on the accuracy of these results. The use of these added technics was associated with more incorrect results on compatible specimens and fewer incorrect results on incompatible specimens. The increase in errors on compatible cross matching was probably due to limited experience with these more complicated technics. These errors are less serious than other types of errors in blood-bank procedures; they might even be classified as "errors in the right direction" and would only eliminate the use of a satisfactory pint of blood. The addition of these technics was associated with fewer incorrect results on incompatible cross matching, because these technics were designed to detect antibody in immunized patients, thus reducing the errors of a potentially more serious nature. These opposing effects, however, do not cancel each other out but should be interpreted as indicating slight improvements in cross-matching results during the study.

A recent brief note states: "The lag time between the development of scientific innovations and their adaptive appearance on the industrial scene is now so very short that technological evolution is difficult to distinguish from revolution."[5] Such rapid use of new developments may well occur in industry, but this study indicates no comparable speed in the use of the newer developments in blood-bank procedures. There appears to be a long lag between developmental research and its use: the actual application of the research findings to the improvement of patient care. The Rh factor was first described in 1939.[6] The early work demonstrating the importance of Rh antibodies in blood transfusion appeared in 1940.[7] The need for albumin or other protein in cross-matching procedures was reported in three publications in 1943 and 1944.[8,9,10] The indirect Coombs test procedure was published in 1945.[11] Materials have been commercially available for these tests since 1948. The value of using all three technics is widely recognized, and yet, in this survey starting in 1958, less than half of the laboratories used all three technics and 16 per cent used only the saline test in the first survey of cross matching (see Table 8). Thus, many of the laboratories were not prepared to detect an immunized patient with the procedure in routine use, which indicates that in these laboratories a cross match was used primarily to detect ABO incompatibility, in essence a test to check the initial ABO grouping procedure. A saline cross match does serve this useful purpose, but in these days when blood transfusion has such wide use, any hospital prepared to give transfusions should be served by a laboratory prepared to detect immunized patients as well as to at least identify $Rh_0(D)$ patients and donors in order to prevent immunization of recipients.

The central and regional training offered prior to and during this study attempted to put modern procedures into wider use. Comparison of ABO and $Rh_0(D)$ results before and after the regional training courses (Table 5) did not indicate significant improvement. Several students who had attended central and regional training courses were still using only the saline technic when cross-matching results were requested in the late surveys. The reasons the training offered had so little influence on test results are not apparent, but comments from the instructors may be pertinent. The wide variation in basic training of students accepted in these courses made it difficult to set the level of instruction to meet the needs of all students. Also it was noted that students with comparatively brief basic education appeared to be reluctant to ask questions when they did not understand instructions, and their reluctance appeared to increase when the class included more fully trained students whose basic education curriculum had included a course in immunology.

The high level of performance by affiliates of the large central blood bank was probably due to the continuity of their training program and the intrinsic follow-up on grouping and typing, both of which antedate the current study. In addition, these affiliates included a slightly larger proportion of large city hospitals, which gives them the added experience from more active transfusion services. Large city hospitals also have more opportunity than smaller hospitals have to hire personnel with good basic education.

The better performance shown by laboratories represented at central and regional training courses as compared with those laboratories from which no representatives received special training may be interpreted in two ways. It may show the influence of training, or it may indicate that the laboratories which chose to send representatives for training had a higher level of performance initially. Probably both these factors are involved.

Continued

TABLE 8
Technics Used for Cross Matching as Reported on Five Surveys

	June 1960 Participants		Sept. 1960 Participants		Dec. 1960 Participants		June 1961 Participants		Sept. 1961 Participants	
Technic(s)	No.	%	No.	%	No.	%	No.	%	No.	%
Saline only	21	16.0	11	9.0	8	6.8	9	8.2	6	5.4
Albumin or indirect Coombs only	14	10.7	11	9.0	7	5.9	6	5.5	10	9.0
Any two of the three technics	32	24.4	30	24.6	30	25.4	15	13.6	16	14.4
All three technics	64	48.9	70	57.4	73	61.9	80	72.7	79	71.2
TOTALS	131	100.0	122	100.0	118	100.0	110	100.0	111	100.0

TABLE 9
Number of Test Results Reported and Number and Percentage of Incorrect Results in Blood Bank Procedures as Associated with Profession or Occupation of Individuals Signing Reports

Groups of Individuals	ABO Grouping			$Rh_0(D)$ Type			Cross Matching					
							Compatible			Incompatible		
	Total	Errors		Total	Errors		Total	Errors		Total	Errors	
Signing Reports	No.	No.	%	No.	No.	%	No.	No.	%	No.	No.	%
Registered M.T.'s(ASCP)	2314	8	0.3	2258	26	1.2	352	23	6.5	219	18	8.2
All other	3777	47	1.1	3673	111	3.0	532	45	8.5	347	114	32.9

Almost half of the actively participating laboratories sent no representatives to training courses even though the results indicated that many needed additional instruction. The reasons for this lack of co-operation with the training program are not known.

Since all large hospitals have comparatively more active transfusion services than others, it is fortunate that the accuracy of test results was better there than in smaller hospitals. This gives assurance that the larger proportion of actual transfusions were served by the laboratories with good performance ratings in this survey.

The value of good basic education in medical technology was well demonstrated by the comparison of performance rating of Medical Technologists with the group of laboratorians with heterogeneous types of training (see Table 9).

The dwindling participation in the study during the three-year period was disappointing. The marked decrease in reports after the addition of cross matching suggests that this additional procedure may have prompted discontinuance in some instances.

The value of this study in extending the availability and improving the accuracy of blood-bank procedures as related to possible needs of the Civil Defense and Disaster Blood Program cannot be measured with confidence. The fact that about 20 per cent of over 450 co-operating laboratorians attended the training courses which were part of the program may have been beneficial, even though improvement in accuracy of results after this training cannot be demonstrated. The increased awareness of accuracy of test performance has probably been of considerable value.

Summary

A total of 200 laboratories of licensed hospitals in Minnesota were potential voluntary participants in a three-year study of blood-bank procedures. In the evaluation of ABO grouping and Rh typing, 154 hospital laboratories participated actively, 31 less actively, and 15 not at all. In the evaluation of cross matching, only 97 hospital laboratories participated actively, 58 less actively, and 45 not at all.

Three or four specimens were distributed in each of 12 surveys, a total of 45 specimens. Reported results totaled over 6400, with 0.9 per cent errors in ABO grouping and 2.4 per cent errors in Rh_o(D) typing. Cross-matching results were requested only during the last half of the study. Results were reported on 908 compatible cross matchings, with 7.5 per cent incorrect results, and on 579 incompatible cross matchings, with 23.3 per cent incorrect results. The high percentage of errors on incompatible cross matchings was associated with the use of only the saline technic in many laboratories; this technic was not adequate for the detection of antibodies in the serum of the immunized patients.

In general, hospital size (number of beds) correlated directly with accuracy of test results and level of participation.

Three types of recent training in blood-bank procedures were available: continuous training to affiliates of a large blood bank, a central training course, or regional training courses available to all participants. In general, accuracy of test results and level of participation correlated with the recent training as follows: laboratories in the continuous training program had the best record, followed by laboratories represented at central, and then regional training courses. The poorest record of accuracy and participation was shown by laboratories from which no representatives attended training courses.

Over 35 per cent of all reports were signed by individuals registered as Medical Technologists; almost 60 per cent were signed by other laboratorians with heterogeneous types of basic education. Accuracy of test results signed by Medical Technologists was significantly better than the accuracy of results signed by other laboratorians. On ABO grouping and incompatible cross-matching results the percentage of incorrect results reported by Medical Technologists was only one-fourth the percentage of incorrect results reported by the individuals with heterogeneous training.

There is a serious time lag between the recognition of new developments in blood-bank procedures and their use in the field. Means should be found to shorten this time lag.

We are indebted to the following for consultation and advice: R. W. Koucky, M.D., Medical Director, G. A. Matson, Ph.D., Director, and Helen Arndt, M. T. (ASCP), Chief Technologist, Minneapolis War Memorial Blood Bank, Minneapolis; N. R. Ziegler, M.D., Ph.D., Immunohematology Consultant, University of Minnesota Hospitals and Ruth Hovde, M.S., M.T. (ASCP), Assistant Professor of Medical Technology, University of Minnesota, Minneapolis; and Glen Taylor, Executive Secretary, Minnesota Hospital Association, Minneapolis.

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Meetings And Announcements

JANUARY — 1964

Woman's Auxiliary, Minnesota State Medical Association, Mid-Winter Board Meeting, January 21, Radisson Hotel, Minneapolis. Contact: Mrs. Leo W. Fink, 6041 Zenith Avenue South, Minneapolis.

American Therapeutic Society and the Minnesota Heart Association Symposium, January 17-18, Radisson Hotel, Minneapolis. Contact: James Kelly, M.D., Minnesota Heart Association, 1821 University Avenue, St. Paul 4, Minnesota.

Minnesota Academy of Ophthalomology and Otolaryngology, Trialogical Meeting at Rochester, Minnesota, January 18-19.

Hahnemann Medical College and Hospital "Cardiovascular Drug Therapy" Marriott Motor Hotel, Philadelphia, January 20-23. Contact: Sage Rosen, 230 No. Broad, Philadelphia.

American Academy of Orthopaedic Surgeons, Palmer House, Chicago, January 18-23. Exec Sec: John K. Hart, 29 E. Madison, Chicago 2.

American College of Surgeons (sectional meeting), Lord Baltimore Hotel, Baltimore, January 27-29. Sec: Samuel J. Harbison, M.D., 40 E. Erie, Chicago 11.

American Protestant Hospital Association, Jefferson Hotel, St. Louis, January 27-31. Dir: Leo M. Lyons, 840 N. Lake Shore Dr., Chicago 11.

Neurosurgical Society of America, Wigwam Hotel, Phoenix, Ariz., January 22-25. Sec: Courtland H. Davis, Jr., M.D., Bowman Gray School of Medicine, Winston-Salem, N.C.
Write: Secretary, Scripps Clinic, La Jolla, Cal.

FEBRUARY

Commission on Drug Safety pilot workshop in Teratology, February 2-8, University of Florida, Gainesville, Florida. Write: Commission on Drug Safety, 221 No. LaSalle St., Chicago.

Annual Convention of Medical Society of the State of New York, February 10-14, The Americana, New York City. Contact the Society.

Sioux Valley Medical Association Symposium Feb. 19-21, Hotel Cataract, Sioux Falls, S. D. Contact: H. E. Rudersdorft, M.D., Sioux Valley Medical Association.

ANNOUNCEMENTS

Applications are now being accepted for the E. V. Allen Memorial Scholarship. Predoctoral and postdoctoral students interested in three months' cardiovascular study at the Mayo Clinic may obtain information from the Minnesota Heart Association, 1821 University Avenue, St. Paul, Minn.

* * *

The next scheduled examination (Part II), oral and clinical, by the American Obstet. & Gyn. Board will be conducted for all candidates at the Edgewater Beach Hotel, Chicago, Illinois by the entire Board, April 27-May 2. Candidates will be sent notice of examination dates.

* * *

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Medical Economics

Farmers Lead in Disability-Illness Work Loss

The average American farmer loses more days of work a year due to illness or injury than any other type of worker.

According to a Health Insurance Institute analysis of data just released by the United States Public Health Service, farmers lost an average of 7.4 days of work per person for the 12-month period ending June 30, 1962. The figure represents 1.7 days more than the city worker who lost 5.7 days on the average during the same period.

Workers in rural non-farm areas had the best over-all average nationwide with 5.3 days a year lost due to disability.

The Public Health Service has offered two reasons for the high-average in work-loss days on the American farm: There is a greater percentage of older persons in farming than in other occupations, and most farm workers have a greater opportunity to postpone a job than is the case in most other types of employment.

The currently employed population — that is, persons 17 years of age or older — of over 68 million, had a total of 394,100,000 workdays lost during the 12-month period for an over-all average of 5.8 days lost per person.

Breakdown by Days

The work-loss days were broken down this way: 343,200,000 workdays lost by the usually employed persons who represent 86 per cent of currently working population; 19 million days lost by housekeeping workers (usually women) who represent seven per cent of workers; and 31.8 million work-loss days were absorbed by persons working at the time the survey was made representing seven per cent of currently employed persons.

By age group, the younger segments of working persons has the lowest average of days lost. For example, the 17-24 group averaged 3.6 work-loss days across the nation while the 25-44 group averaged 5.0 days per currently employed person, said the Institute.

Persons between the ages 45 and 64 averaged 7.3 days lost, while persons 65 and over in the nation averaged 8.0 days.

Except for the 17 to 24 age group, farmers had the highest average number of work-loss days in all other age categories. In the 25 to 44 group, farmers lost an average of 6.4 days a year while urban workers lost 5.1 days. In the 45 to 64 category, 9.5 work-days were lost by farmers and 7.0 days by city workers. In the 65 and over group, farmers averaged 12.1 days lost a year and urban workers 7.2 days.

Federal Spending May Curb Academic Freedom

The rights of medical schools may be in danger of being "whittled away by the rules and regulations" of federal grants now supplying fifty per cent of their support, John M. Russell, President of the John and Mary R. Markle Foundation said in the annual report of the fund recently.

"The picture of government spending has been developing a dreamlike quality of peace and comfort, with the federal government

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taking the form of a mother image to the suckling medical schools. Even though well over half of medical school budgets come from federal sources, fears of government control" are regarded by many schools as "silly." "They can show that scientists are consulted about distribution of grants; that top government experts understand the problems of medical schools; and that medicine and health have friends in Congress. But the 'freedom' now permitted under federal grants may soon become a snare and a delusion. Policy formation in our government is at so many levels and by so many people, it may take more than wishful thinking in the White House to keep the rights of medical schools, research laboratories and teaching hospitals from being whittled away by a rule here or a regulation there."

The report recommends that "an effective means be found so that those responsible for academic medicine in the United States have something to say about the conditions under which they will be working as federal grants increase and openly begin to support medical education as well as research. This will take some hard, thoughtful, courageous action by those in academic medicine. The business of protecting academic freedom from any donor — public or private — is no joke."

Academic Popularity Contest

Rapid growth of budgets have shown the need for skilled administrators in medical schools, yet the dean seems to occupy "the low place in the spectrum of respect and honor."

"The type of activity — research, teaching, clinical work or administration — that constitutes success in academic medicine seems to change with the years. Once the great clinician-teacher drew all the kudos; today, it is the research man who publishes innumerable papers; tomorrow, the type of man at the top is anyone's guess. This sort of academic popularity contest, with its built-in distortion of values and its snob appeal, has no place in academic medicine." Today, "the low place" is held by the dean, despite the fact that "medical school administration is no longer a petty operation. The budgets in some cases exceed those of many universities. Much of this money comes in the form of grants to support the work and often the salary of individual faculty members. This adds fuel to the conflict between the personal interests of the faculty member and his responsibilities to the medical school as a whole. Complexity of medical school administration has developed because of the sudden, fantastic growth of budgets, mostly from grants and gifts for medical research, mainly from public sources . . . Scholars have always jealously guarded their freedom, but now they must recognize the need to work together under strong leadership, for medical schools cannot survive under administrative chaos in these days of complex budgets."

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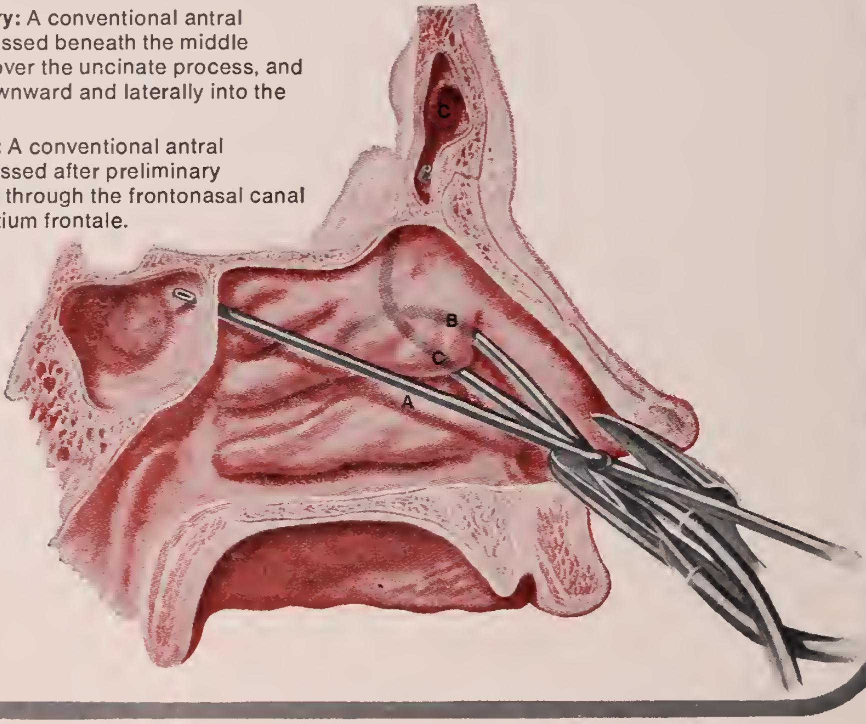

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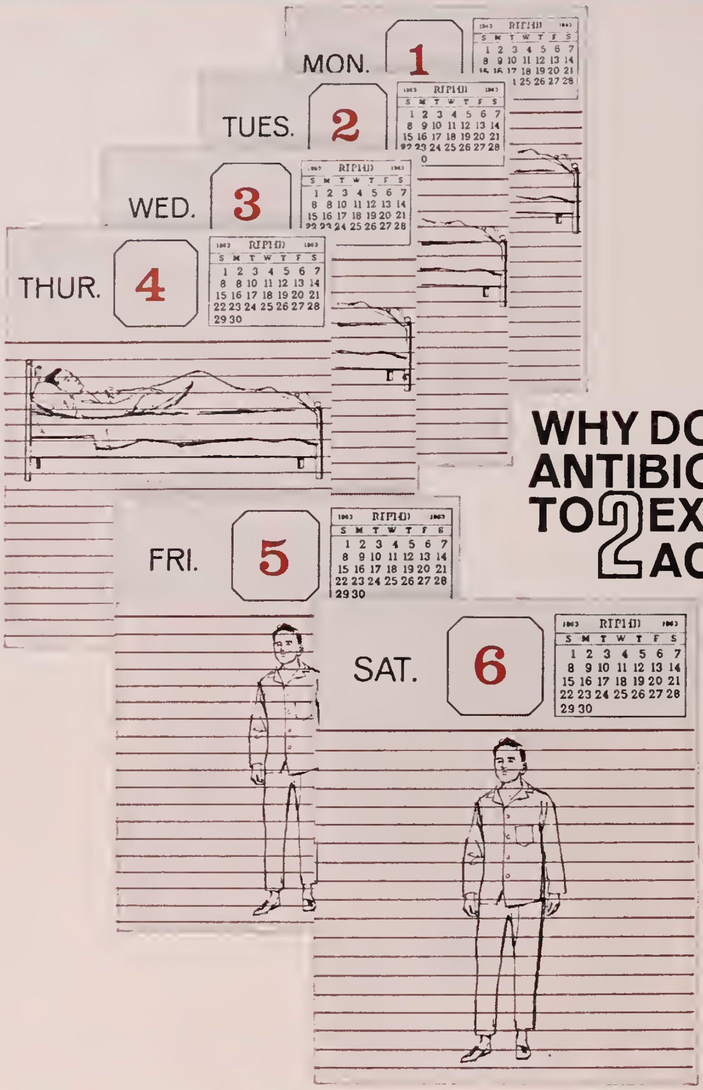

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President's Letter

As you all know, an Act was passed at the last session of the Legislature of the State of Minnesota relating to the practice of medicine and osteopathy. The passage of this legislation was a great step toward solution of a long, contentious and expensive difference between members and other supporters of the involved schools of practice.

To review briefly, a committee was appointed about two years prior to the enactment of the law by the governor of that time to study the problem. The committee was composed of three doctors of medicine, three doctors of osteopathy and a neutral chairman. The committee functioned well. After several meetings and after approval of the Minnesota State Board of Medical Examiners, the committee influenced the House of Delegates of the Minnesota State Medical Association and the Minnesota State Osteopathic Association late in 1962, to support the legislation adopted in 1963. As a matter of personal opinion, I think that the legislators were also relieved to support the bill which promised resolution of the controversy which had taken up such an inordinate amount of their time and attention for so many sessions.

Many persons deeply involved are still poorly informed regarding the present status in regard to the entire matter, however, and clarification seems to be in order.

As of May 1, 1963, the former Board of Osteopathy was abolished. On that date a new Minnesota State Board of Medical Examiners was created and so designated. A doctor of osteopathy was placed on the Board which has a membership of seven doctors of medicine and one doctor of osteopathy. Hereafter a person holding the degree of Doctor of Medicine or Doctor of Osteopathy, not already authorized to practice in the State and desiring to do so, shall apply to the State Board of Medical Examiners for examination. Those accepted for examination after meeting the moral and educational requirements, and those who successfully pass the examination, will be granted licenses to practice *medicine* in the State. Specifically, successful candidates who have graduated from medical or osteopathic schools will be practicing under the same type of licenses in Minnesota. The act does not mention the situation in regard to hospital staff appointments.

No new licenses for the practice of osteopathy are to be granted, though those who now hold such licenses may continue to practice osteopathy under the jurisdiction of the present Board of Medical Examiners. Provision has been made by the Legislature for any doctor of osteopathy, presently licensed in Minnesota under the old Statutes, to obtain a license to practice medicine upon application to the Board of Medical Examiners and successful completion of examinations in those subjects in which he was not examined by the State Board of Osteopathy prior to the issuance to him of his present license.

One of the provisions of the Act under

Continued on Page 169

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Tobacco

in Cardiovascular Disease*

ALEXANDER SCHIRGER, M.D.**
RICHARD M. SHICK, M.D.**
Rochester, Minnesota

THE EFFECTS of tobacco in cardiovascular disease can be considered from three arbitrary viewpoints: (1) peripheral vascular disease, arterial or venous, (2) heart disease, coronary or other, and (3) hypertension, malignant or benign.

Although much has been written in recent years about the various effects of tobacco in these disease states as well as about the possible relationship of the use of tobacco to their development in the future, we shall consider the matter only from the standpoint of the everyday practice of medicine. What does the physician tell his patients in the office when asked the ever-recurring question, "What about tobacco?" The question really should be, "What about nicotine?" since this is the vasoactive substance in tobacco smoke. Nicotine is a potent peripheral vasoconstrictor; it decreases peripheral blood flow both in normal persons and in patients with occlusive arterial disease. Furthermore, it increases blood pressure, pulse rate and cardiac output. Experimentally, when the coronary circulation is compromised, administration of nicotine increases cardiac output without commeasurable increase in coronary blood flow, so that coronary insufficiency occurs. The effects of smoking on the cardiovascular system of man have been reviewed in detail by Roth and one of us.[1]

Tobacco in Peripheral Vascular Disease

The ability of nicotine to produce strong peripheral vasoconstriction has long been observed physiologically and clinically. Consequently, for many years physicians have, with more or less persuasiveness, advised patients not to use tobacco when afflicted with a peripheral arterial disorder.

Thromboangiitis Obliterans

One of the most striking effects of tobacco observed clinically is that seen in thromboangiitis obliterans, or Buerger's disease; continued use of tobacco apparently exerts a deleterious effect on the disease. In a recent study of thromboangiitis obliterans in South Korean young men free of atherosclerosis, McKusick and Harris[2] found that all of them had a history of prolonged and excessive intake of tobacco.

---

*Read at the meeting of the Minnesota State Medical Association, Minneapolis, Minnesota, May 21 to 23, 1962.

**Section of Medicine, Mayo Clinic

In recent years the existence of this entity[3] has been questioned, but Barker[4] has clearly summarized arguments against the view. No physician should be misled by the current debate to the extent that he fails to make categoric recommendations to patients afflicted with the disease: complete and permanent abstinence from the use of tobacco in any form is imperative and remains the most important single factor determining the ultimate outlook.

TABLE 1
Tobacco in Peripheral Arterial Disease

Disease	Recommendations
1. Thromboangiitis obliterans (Buerger's disease)	Tobacco strictly prohibited
2. Arteriosclerosis obliterans	Tobacco strictly prohibited
3. Occupational occlusive arterial disease of hands	Tobacco strictly prohibited
4. Vasospastic arterial disease a. Raynaud's disease b. Raynaud's phenomenon secondary to other conditions (scleroderma)	Individualized according to severity of symptoms; use prohibited if complications are present

TABLE 2
Tobacco in Peripheral Venous Disease

Disease	Recommendations
1. Acute iliofemoral thrombophlebitis	Use of tobacco restricted to avoid increase of arterial spasm which may be present during initial stage
2. Recurrent diopathic thrombophlebitis	Opinions vary; categoric interdiction of use of tobacco cannot be justified unless strong suspicion exists that thrombophlebitis is initial manifestation of thromboangiitis obliterans

TABLE 3
Tobacco in Coronary Heart Disease

Type of Disease	Recommendations
a. Acute myocardial infarction	Tobacco prohibited
b. Acute coronary insufficiency (prolonged myocardial ischemia without infarction)	Tobacco prohibited
c. Severe angina pectoris of effort and of rest	Tobacco prohibited
d. Mild-to-moderate angina with anginal pain after smoking	Tobacco prohibited
e. Mild angina in older patients who have pain only rarely after unusual effort	Moderate use of tobacco probably permissible

Arteriosclerosis Obliterans

While for years physicians felt justified in recommending that patients with arteriosclerosis obliterans curtail or abstain from the use of tobacco, some tended toward sympathetic permissiveness in regard to moderate use for patients free of ischemic complications such as ulceration, ischemic neuropathy, and nocturnal rest pain. However, in a recent study, Juergens and coworkers[5] found that, when the follow-up period was sufficient, nondiabetic patients with arteriosclerosis obliterans who continued to smoke had an approximately 10 per cent chance of requiring subsequent amputation, while none of the nonsmokers required it. We believe that the use of tobacco should be interdicted in any patient with a diagnosis of arteriosclerosis obliterans. Patients usually readily accept this small sacrifice when informed that continuance of smoking will increase the probability of amputation in the future.

Occupational Occlusive Arterial Disease of the Hands

The patient with occupational arterial disease of the hand may have occlusion of the radial or ulnar artery or of the palmar arch. We recommend for such a patient complete abstinence from the use of tobacco in conjunction with protection from and avoidance of the etiologic occupational trauma. When these two recommendations are followed, sufficient collateral circulation may become established to avoid the need for sympathectomy in the future.

Vasopastic Arterial Disease

In patients with so-called vasopastic arterial disease, recommendations should be individualized according to severity of symptoms. In general, it is advisable that patients with Raynaud's disease and with Raynaud's phenomenon secondary to other conditions such as scleroderma abstain from the use of tobacco. However, continued use in moderate amounts during asymptomatic periods would not seem unreasonable for the patient who only rarely experiences a vasospastic episode, perhaps during extremely cold weather in winter, who is not bothered during ordinary daily activities, and who is asymptomatic throughout most of the year. If, however, complications of repeated vasospastic episodes are present, such as ulcerations or paronychial infection, use of tobacco should be strictly prohibited.

Peripheral Venous Disease (Table 2)

It has been our custom during the initial period of hospitalization to advise patients with acute iliofemoral thrombophlebitis to restrict the use of tobacco in order to avoid enhancement of any arterial spasm that may be present. Once the acute thrombophlebitis has subsided, use of tobacco need no longer be restricted.

Opinions vary as to the importance of discontinuing smoking in so-called recurrent idiopathic thrombophlebitis. However, it would seem at this time that categoric interdiction cannot be justified unless strong suspicion exists that recurrent thrombophlebitis is the initial manifestation of thromboangiitis obliterans. Since we allow a period of two to three years of observation before establishing the diagnosis of recurrent idiopathic thrombophlebitis with finality, the question about need for interdiction of the use of tobacco arises only during the early months after the repeated thrombophlebitic episodes make their appearance.

Tobacco in Heart Disease

Coronary Diseases

Patients with coronary heart disease (Table 3) who are convalescing from acute myocardial infarction, or who have acute coronary insufficiency with electrocardiographic evidence of prolonged myocardial ischemia, but whose condition does not progress to the final event of myocardial infarction, should be advised to avoid completely the use of tobacco. The most compelling reason for this recommendation would seem to be the potentiation of an already increased irritability of an injured heart muscle. This consideration would seem to take precedence over the fact, of no little importance, that smoking increases blood pressure, heart rate and myocardial work. For these same reasons, we advise patients with severe angina pectoris of effort and of rest to discontinue the use of tobacco completely. It likewise seems reasonable that patients who have mild to moderate angina and experience anginal pain after smoking should be advised not to smoke. On the other hand, some older patients with coronary heart disease who have mild angina and who experience pain only rarely after unusual exertion probably need not be dissuaded from the moderate use of tobacco which has become their habit over many years and may add to their enjoyment of life.

Other Heart Disease (Table 4)

Recommendations regarding use of tobacco for patients with other than coronary heart disease need to be individualized. Those who experience paroxysmal atrial tachycardia and frequent persistent premature contractions should be advised, at least for a time, to discontinue the use of tobacco completely. In some patients, this measure alone may diminish the frequency of attacks and ameliorate their symptoms; unfortunately, even patients who do follow this advice faithfully and with perseverance may not benefit from abstinence, and for them resort to other measures will be needed. Then the physician must decide whether, when satisfactory control has been achieved by one of the prescribed medical programs, the use of tobacco can be allowed.

We generally do not categorically advise patients with chronic atrial fibrillation of long standing to discontinue the use of to-

TABLE 4
Tobacco in Other Diseases of the Heart

Disease	Recommendations
1. Rhythm disturbances	
a. Paroxysmal atrial tachycardia	Tobacco prohibited
b. Frequent symptomatic and persistent premature contractions	Tobacco prohibited
c. Chronic atrial fibrillation	Moderate use reasonable
2. Valvular heart disease	Individualized
3. Acute myocarditis	Tobacco prohibited
4. Pericarditis	
a. Acute	Tobacco prohibited
b. Chronic constrictive pericarditis	Individualized

bacco. In patients with valvular heart disease, recommendations should be individualized, depending on the severity of symptoms and on the hemodynamic significance of the valvular lesions as well as on the presence or absence of symptoms of decreased myocardial reserve. For reasons mentioned in the discussion of patients with acute myocardial infarction, complete abstinence from the use of tobacco seems prudent in those individuals afflicted with acute myocarditis or acute pericarditis, in the latter instance because the epicardium may also be involved.

Hypertension

One of those who most often ask, "What about tobacco?" is the patient with hypertension. No definite recommendation can be made to such patients. Obviously, for the patient with malignant or the accelerated phase of hypertension the physician needs to use his judgment in deciding whether to allow smoking, to advise restriction, or to recommend complete abstinence from the use of tobacco. When coronary heart disease is present, the recommendations outlined previously apply. Evidence seems insufficient to justify advising categorically that use of tobacco be restricted in those individuals with mild to moderate uncomplicated hypertension who smoke moderately. As to patients with labile hypertension, the so-called vascular hyperreactors, who may have normal resting systolic and diastolic pressures but who are hypertensive at other times, very few become normotensive after discontinuing the use of tobacco.[6]

Conclusion

While the answer to the question, "What about tobacco?" in the conditions discussed must often be in the negative, regret over restriction of its use should be mitigated by the fact that a candid answer without equivocation will be in the patient's best interest.

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TINEL'S SIGN
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Tapping the nerve trunk below the site of the nerve lesion or laceration produces distal tingling. This sign is done several months after the nerve has been injured to indicate whether recovery of the nerve is taking place. If this place is marked at regular intervals the rate of regeneration can be demonstrated in this manner.

Ashes to Ashes

If you insist on smoking in bed, the ashes you drop may be your own.—Jack Paar

---

A jest breaks no bones.—Samuel Johnson

Measles Virus Vaccination

WARREN WARWICK, M.D.
Minneapolis, Minn.

MEASLES IS the greatest killer and crippler among the communicable diseases of childhood. Each year close to 600 deaths are attributed to measles in the United States. The serious complications of measles occur principally in the respiratory tract and the brain. Deaths from bronchopneumonia and encephalitis occur in all strata of society. The annual number of these deaths has exceeded the deaths caused by polio in even its worst epidemic years.[1]

Measles has been an especially severe disease in children with chronic pulmonary diseases such as tuberculosis or cystic fibrosis; large numbers of such affected children succumb to the complicating bronchopneumonia. In areas of the world where protein deficiency and malnutrition are common the mortality rate for measles may be as high as 20 or 25 per cent.[2]

There is one case of clinically apparent measles encephalitis per hundred cases of measles. However, the incidence of encephalitis as detected by electroencephalogram is in excess of 50 per cent of cases. Many of the behavior disorders of childhood have been attributed to measles encephalitis. The sequelae of measles encephalitis include psychiatric disturbances, abnormalities of muscular function and abnormalities of mental function.[3]

Although these facts are known to the medical community, they are not known to the average parent who thinks of measles as merely one of the common diseases that all his children will have. A review of these facts should serve as sufficient indication for physicians to emphasize the need for every child who has not had measles to receive measles virus vaccination. They should also provide convincing evidence to any parents who do not understand the need for other immunizations beyond the "baby shots."

The currently available live attenuated measles virus vaccine has been shown to be effective in producing immunity to the native measles virus by numerous methods. About 95 to 100 per cent of patients who were immunized with the live attenuated measles virus vaccine developed an immunity which could be detected by either complement-fixing or virus-neutralizing systems. This high conversion ratio was also found when live attenuated measles virus vaccine and gamma globulin were given at the same time but with separate syringes at separate sites. With or without gamma globulin, the live attenuated measles virus vaccine has been shown to be 97 per cent effective in preventing measles when immunized children have been compared with unimmunized children during an epidemic season. In fact, this immunization against measles has proven effective when given as late as the time of exposure to a proven case of measles.[4]

There have been no serious complications from the use of the live attenuated measles virus vaccine, although when it was given without concurrent gamma globulin a high proportion — about 30 per cent — of the children had a febrile episode. In most children the fever has usually been mild; however, about half of the children who reacted to the immunization had either a fever up to 103° F. for one or two days or a skin rash of modified measles.[5]

When the measles virus vaccine has been given with gamma globulin there is a sharp reduction in the frequency of the clinical reactions, but the intensity of the immune response appeared to be the same in each group. However, when individual children are considered, a high degree of immunity developed in those children who had a fever of 101° F. or greater than in those children who had no fever.[6,7]

None of the children who have been immunized with the live attenuated measles virus vaccine have developed pulmonary or central nervous system complications. This is true even in the children with cystic fibrosis who are inordinately susceptible to this complication of the native measles virus.[8]

Moreover, none of the many thousands of children who have received the live attenuated measles virus vaccine have shown any encephalitic type of reaction. This was to be expected, however, for detailed electroencephalographic studies done on institutionalized patients who received live attenuated virus vaccine have shown no abnormalities in their electroencephalograms.[8]

The duration of the protection offered by the live attenuated measles virus vaccine is unknown. Protection has been demonstrated for several years. Even children who have received the live attenuated measles virus vaccine and who have had a later drop in serum antibody titre have responded with an increase in titre after exposure to a case of measles even though they had no signs of the disease.[4]

Immunization with the live attenuated measles virus vaccine in combination with gamma globulin is safe, simple, and effective. It is the method of choice for measles immunization for almost all persons over seven months of age who have not had measles. There are but few exceptions. The live attenuated measles virus vaccine should not be given following gamma-globulin prophylaxis during the previous six to eight weeks, since the remaining gamma globulin may inactivate the vaccine. Persons who are allergic to eggs or egg products should not be given the live attenuated measles vaccine. Any disease or therapeutic state which may depress the patient's resistance is a contraindication to the live attenuated measles virus vaccine. Examples are: severe febrile illnesses, tuberculosis, generalized malignancies, leukemia, lymphomas and treatment with corticosteroids, radiation, alkalating agents and antimetabolites.

Since patients in the groups listed above may be as susceptible, if not more susceptible, to the severe complications of measles, it is fortunate that there is a killed measles virus vaccine which they may receive. One of the killed measles virus vaccines is grown in monkey kidney tissue,[5] another on chick embryos.[9] Both have a lower incidence of reactions than the live attenuated measles virus vaccine. A single injection of the killed measles virus vaccine is less effective than the live attenuated measles virus vaccine.

However a series of three injections of the killed measles virus vaccine appears to give equivalent antibody response and protection upon exposure to an acute case of measles.[9,10]

An alternative immunization program which will be preferred by some physicians will begin with three doses of the killed measles virus vaccine. Since this vaccine is compatible with the triple vaccine, diphtheria, pertussus, and tetanus, the immunization could begin in the first months of life. This program would be completed by giving the live attenuated measles virus vaccine.

It is hoped that the use of both vaccines, the live attenuated measles and the killed measles virus vaccine, will be accepted for widespread general use both by the medical profession and by the general public. If so, this could eliminate between five to six hundred deaths and five to six thousand cases of encephalitis caused by measles each year in the United States. If so, the day may come when Koplik's spots will be as rarely seen as the membranous exudate in diphtheria.

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Galen's Materia Medica*

Diseases of the Eye

For cataracts he recommends a mixture of equal parts of mouse's blood, cock's gall and women's milk (dried). For a sty in the eye, catch flies, cut off their heads and rub the sty with the rest of their bodies.

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*Thorndike, Lynn — see Minn Med Oct. '63.

Americanism

If you want your father to take care of you, that's paternalism. If you want your mother to take care of you, that's maternalism. If you want Uncle Sam to take care of you, that's Socialism. If you want your comrades to take care of you, that's Communism. But if you want to take care of yourself, that's Americanism.

— Rotamoor

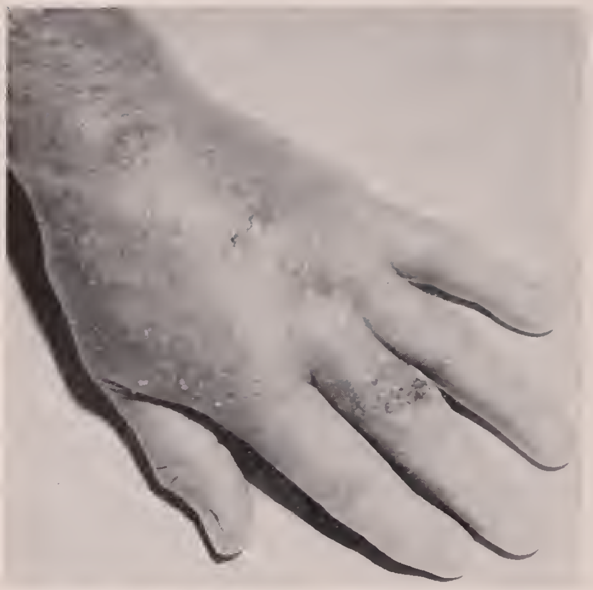

Fig. 2 — Closeup of hand showing in detail the chancriform lesion on the first phalanx of the third finger with granulation tissue at the base of the ulcer and the nodules on the hand and wrist.

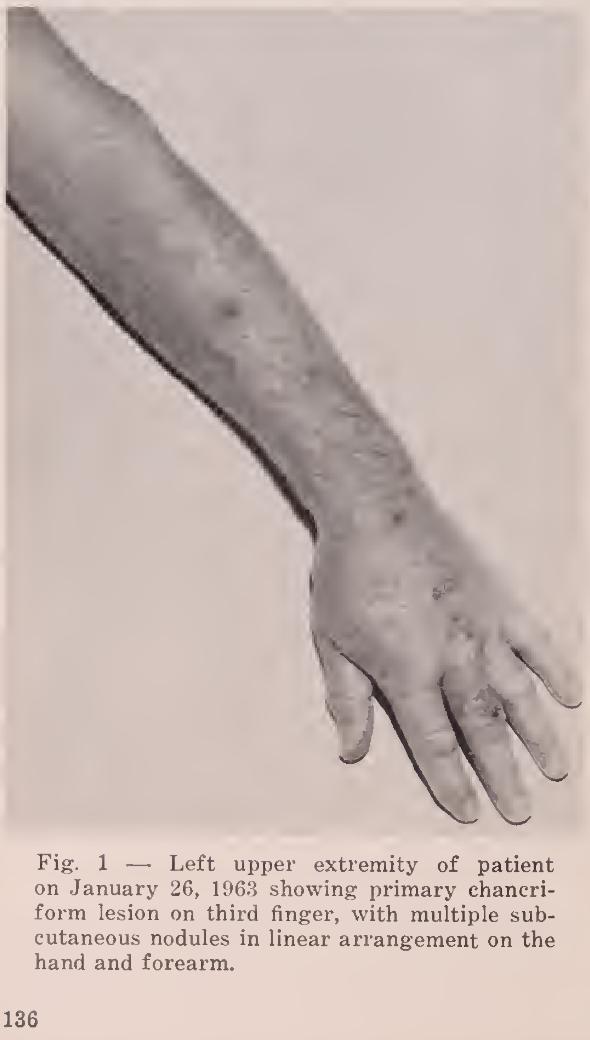

Fig. 1 — Left upper extremity of patient on January 26, 1963 showing primary chancriform lesion on third finger, with multiple subcutaneous nodules in linear arrangement on the hand and forearm.

Sporotrichosis

SPOROTRICHOSIS, in contrast to most other deep fungous infections, usually follows the direct inoculation of the causative organism, Sporotrichum schenckii, through the skin by means of puncture wounds. From one week to a few months after inoculation, a characteristic clinical pattern develops consisting of a chancriform lesion at the site of the wound, associated with subcutaneous nodules and ascending lymphangitis of the involved limb. The upper extremity is most frequently involved. Less frequently, probably depending on the immune state of the patient and the site of inoculation, a generalized type of infection involving the skin and viscera or, rarely, the viscera alone, may occur. The systemic administration of iodides causes a dramatic response of this fungous organism and usually results in cure of the disease. Spontaneous regression of cutaneous and systemic lesions does not occur.

The purpose of this article is to present a case of primary cutaneous sporotrichosis and

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*Read at the meeting of the Southern Minnesota Medical Association, Rochester, Minnesota, September 9, 1963.

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An Important Fungous Disease In Minnesota

to emphasize the occurrence of this disease in the Mississippi Valley and the state of Minnesota.

Case Report

A 69-year-old retired electrician from the Midwest was first seen at the Mayo Clinic on January 26, 1963, with skin lesions of two months' duration. During early November, 1962, he had pruned the rose bushes in his garden, but he could not recall any injury to the skin. By the end of the month, he noted a "red pimple" on the dorsal aspect of the third left finger at the level of the first phalanx. Five days later, the lesion was one cm. in diameter and ulcerated; blood and pus exuded from it. Pain was minimal. After one week the finger and the left hand, wrist, and forearm became swollen and slightly tender.

The patient was hospitalized elsewhere. His physician reported that in addition to the ulcer on the finger, the patient had lymphangitis of the left upper extremity. Axillary adenopathy was absent, however. Two cultures of material from the primary skin lesion on the finger showed Pseudomonas aeruginosa, which was sensitive to polymyxin B and to neomycin. Treatment with wet dressings, bacitracin ointment, and systemic administrations of penicillin, colymicin, and polymyxin B was unsuccessful. Fungous cultures from the skin did not show growth after two weeks.

Despite the rather violent skin reaction, the patient's health remained good. On January 14, 1963, he noted subcutaneous nodules on the dorsal aspect of the left hand and the extensor aspect of the left forearm.

Physical Findings

On examination the abnormal findings were limited to the left upper extremity (Fig. 1) where an ulcer two cm. in diameter with irregular surelevated, indurated borders presented on the dorsal aspect of the first phalanx of the third finger (Fig. 2). The base of the ulcer was covered with granulation tissue and small pustules were present at its periphery. Swelling of the hand prevented complete flexion of the fingers. About 15 small red-purple superficial nodules, some ulcerated, appeared on the extensor aspect of the hand and forearm. Along the internal border of the biceps brachii, about 15 nontender nodules, some mobile and others fixed to the deep tissues, were also observed, all nodules arranged linearly along the left extremity with linear induration along the lesions.

Clinical Appearance

The clinical picture was that of cutaneous sporotrichosis of the lymphatic type. A punch biopsy of a lesion of the forearm showed a histologic pattern of chronic granuloma in the dermis. Another portion of the specimen was inoculated into hormone blood agar and dextrose agar media at room temperature (22° to 24° C.) and at 37° C. General laboratory tests including a roentgenogram of the thorax, urinalysis, determination of hemoglobin, leukocyte and differential counts, and a serologic test for syphilis were within normal limits or without evidence of abnormality.

Potassium Iodide Treatment

On the basis of the typical clinical findings for sporotrichosis, treatment with one gm. of potassium iodide daily was started on January 26; over the next five days the dose was increased gradually to two gm. three times a day.

The Cultures

Because the first culture for fungi was negative the sixth day after inoculation, another culture was taken from tissue of the primary lesion on the finger. On the sixth day of growth of the second specimen, the cultures were positive for Sporotrichum schenckii. At room temperature on dextrose agar, the colonies appeared as a moist adherent creamy white mat. In five additional days, the surface became wrinkled, and a brown to black pigment had appeared (Fig. 3*a*). Increased pigmentary changes occurred as the colony became older. After six days on hormone blood agar, the colonies were velvety and showed definite filaments (Fig. 3*b*). Daily observations of microculture of one of these colonies on dextrose agar at room temperature revealed the presence of septate mycelia and clusters of pyriform conidia at the tips of short conidiophores (Fig. 4). A few conidia free from their sterigma could be seen.

At 37° C. on hormone blood agar, the yeast-phase type of colony was observed with a smooth, white, satiny appearance which might be confused with a bacterial colony of Staphylococcus aureus. The irregularity of its contour, however, was suggestive of Sporotrichum schenckii.

The End Result

The patient was dismissed from the clinic on February 7. The edema of the hand had decreased and flexion and extension of the fingers had increased. Continued treatment with potassium iodide, two gm. three times daily, was prescribed.

After one month of iodide therapy, the patient noted an asymptomatic maculopapulopustular eruption on his scalp, forehead, face, shoulders, and chest. Gastrointestinal symptoms, salivary gland swelling, and photophobia did not occur. The eruption was considered to be secondary to the iodide, and use of the drug was stopped for one week. Iodides were given again, the total daily dosage being three gm.

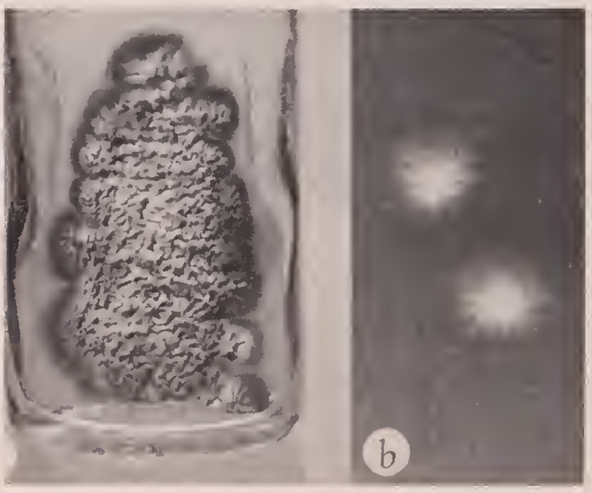

Fig. 3*a* — Sporotrichum schenckii. Culture on dextrose agar at room temperature 11 days after inoculation shows brown pigment and wrinkled surface. b. Sporotrichum schenckii. Culture on hormone blood agar at room temperature six days after inoculation. This mycelial phase is velvety in appearance with definite filaments.

On re-examination of the patient at this clinic on May, 7, 1963, the eruption secondary to iodide therapy still persisted but to a lesser degree. No trace of the original skin lesion was apparent on the left upper extremity, but a small scar could be seen on the third left finger (Fig. 5 and 6). Flexion and extension of the hand were improved with physical therapy. The administration of potassium iodide was discontinued.

Comment

The fungous infection caused by Sporotrichum schenckii was first described by Schenck in 1898.[1] In France, beginning in 1906, De Beurmann and Gougerot[2,3] wrote extensively on the subject, particularly on the disseminated form of the disease which seemed to occur more frequently in Europe than in the United States. In this country Foerster,[4,5] Moore and Kile,[6] Collins,[7] and Cawley[8] were responsible for documentation of this disease. Up to 1944, Sporotrichum schenckii present in timber was found to cause characteristic lesions in a total of 2825 workers in the mines of the Witwatersrand in South Africa.[9] In 1957, Duran, Coventry, Weed, and Kierland[10] reported 23 cases of sporotrichosis and emphasized the localization of the primary lesion on the upper extremity.

Missouri-Mississippi River Basin Endemic

Every American author pointed out that sporotrichosis was almost endemic in the Mississippi Valley. Foerster,[4,5] in an analysis of 148 reported cases, found that 130 of the patients lived in the Missouri-Mississippi River basin. In a review of 39 cases encountered in this institution, eight patients were from Minnesota. The last patient with the disease seen at this clinic in July 1963 was a woman from a farming community in southeastern Minnesota. We must appreciate that sporotrichosis is endemic in Minnesota and we need to recognize the disease in its usual and atypical forms.

Thorns, Moss, Hay

Infection with the organism causing sporotrichosis has been observed following injury from timber in mines, thorns of the barberry shrub and rose bushes, sphagnum moss (used to pack pine trees in nurseries), salt meadow hay (used to mulch tulip bulbs or to cover asphalt tennis courts), sawdust (mixed with sand and used for icy roads), and straw (used to wrap bricks for shipment). Cases have been attributed to rat and mouse bites and to scratches by rabbits and gophers. It is not surprising, therefore, to see this disease among farmers, horticulturists, florists,[11] road workers, and miners.

Cutaneous Manifestations

The commoner primary cutaneous localized lymphatic form should be diagnosed readily by the alert clinician. A chancriform wound with regional lymphangitis but without lymphadenopathy or fever that develops after injury with a thorn, a plant, or a timber, should immediately suggest sporotrichosis. If, in addition, nodules are seen along the draining lymphatics, the diagnosis is almost certain, although one should also think of other deep fungous infections, yaws, nodular leprosy, American leishmaniasis, tularemia, and squamous cell carcinoma.

Seldom will the organism be found in exu-

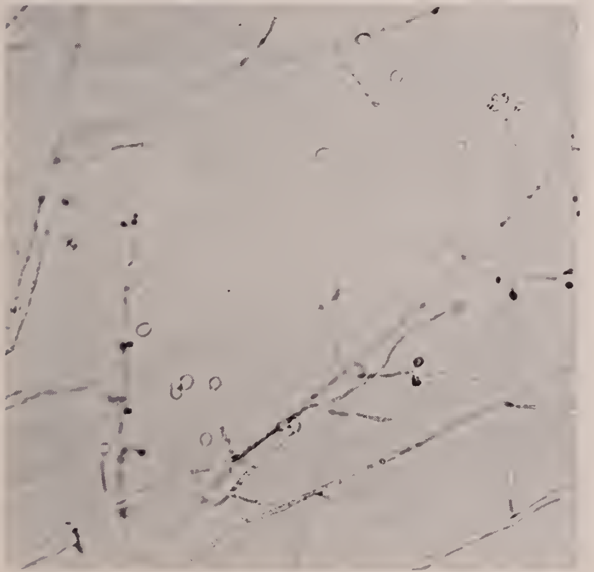

Fig. 4 — Sporotrichum schenckii. Microscopic subculture on dextrose agar at room temperature showing the septate mycelia, the conidiophores and, at their tips, clusters of pyriform conidia with a few conidia free from their sterigma.

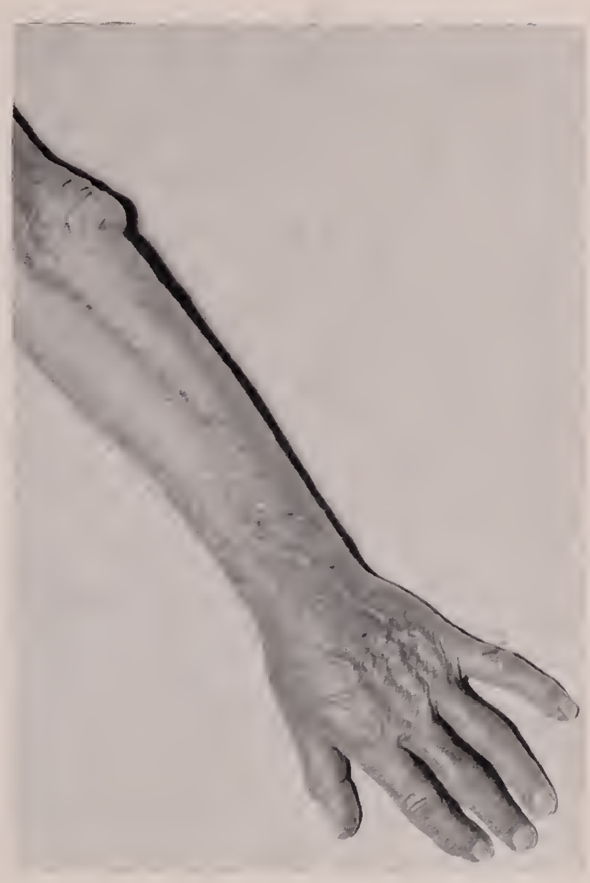

Fig. 5 — Left upper extremity of patient on May 7, 1963, showing complete regression of the cutaneous lesions.

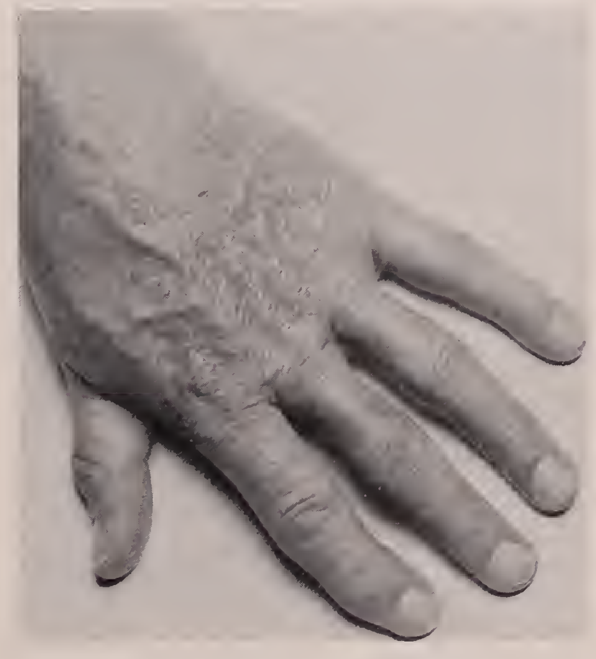

Fig. 6 — Closeup of hand on May 7, 1963. Only a mild erythema is seen at the level of the primary lesion of the third left finger.

dates of the lesions or in tissue sections on microscopic examination. Fortunately, however, it will grow readily on adequate culture media. In the case presented, even though cultures taken elsewhere and our own first cultures were negative for fungi, culturing on special hormone blood agar resulted in growth of Sporotrichum schenckii. The smooth, white colonies obtained at 37° C. may be misinterpreted as colonies of Staphylococcus.

Potassium Iodide Specific

The treatment of sporotrichosis, especially the localized form of the disease, with potassium iodide can be accomplished with the patient ambulatory and unhospitalized and is uniformly successful. Regression of the lesions will be noticed within a week. The disseminated form of the disease does not always respond to iodides. The mechanism of the action of the drug is unknown. The physician needs only to make sure that the drug is well tolerated. At first small doses should be given several times a day; later the dosage should be increased progressively; Utz[12] recently suggested a dose of two gm. four times a day. The drug should never be given on an empty stomach. To prevent any relapse of the disease, treatment should be continued for at least four weeks after clinical findings have disappeared.

Gastrointestinal intolerance, photophobia, conjunctivitis, and swelling of the salivary glands may occur. Anaphylactic reactions have been rare. Polymorphic skin reactions, such as were observed in our patient, occur infrequently. When reactions do occur, use of the drug should be discontinued for one or two weeks and then reinstituted at a lower dosage.

Sodium iodide may be given intravenously when potassium iodide is not tolerated by mouth. Some authors[13] have given antihistamines in conjunction with as much as 12 gm. of potassium iodide daily without reaction. Solutions of potassium iodide may be used locally in conjunction with the systemic route. The new antifungal antibiotics (amphotericin B and X-5079 C) need not be used in the primary cutaneous localized forms of the disease, since potassium iodide is so effective. Grieseofulvin has been tried with doubtful results.[14]

Summary and Conclusions

Sporotrichosis in its primary cutaneous form usually follows the direct inoculation of the causative organism through the skin by means of puncture wounds.

A presumptive diagnosis of this infection can be made on the clinical appearance of a chancriform lesion and on ascending lymphangitis in which subcutaneous nodules are present. A definite diagnosis is established by cultures showing characteristics of Sporotrichum schenckii.

Colonies that appear as moist, adherent, creamy white mats, becoming wrinkled and pigmented, are seen on dextrose agar medium at room temperature some six to 12 days after inoculation. The mycelial phase type of colony is seen on hormone blood agar at room temperature six days after inoculation. Microscopic subculture of one of these colonies on dextrose agar at room temperature may reveal the presence of septate mycelia and clusters of pyriform conidia at the tips of short conidiophores. The yeast-phase type of colony is observed at 37° C. on hormone blood agar.

To be emphasized is the fact that this disease commonly occurs in the Mississippi Valley States including Minnesota. Patients having sporotrichosis can be treated successfully with oral administrations of potassium iodide.

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WHAT'S YOUR DIAGNOSIS?

A sixty-five-year-old white female entered the hospital with a four-hour history of acute severe epigastric and precordial pain which radiated into the neck. There was dyspnea but no nausea or vomiting. Past history was relevant in that the patient had cardiovascular hypertension but was not receiving medication.

On examination, the woman was writhing in severe pain, diaphoretic, and pale. Pertinent findings were that the lungs had bilateral crepitant rales, the heart was of regular rhythm and tones were distant. A grade 2/6 localized systolic murmur was auscultated in the fourth left intercostal space. The abdomen was soft, without bowel tones or masses. All peripheral pulses were present but weak in the distal areas. The blood pressure was 120/60 (right arm) and 180/110 (left arm) mm. Hg.

The chest roentgenogram suggested left heart enlargement, minimal pulmonary congestion, and calcium in the aorta. An electrocardiogram depicted a left ventricular hypertrophy pattern and depression of the ST-T segments.

Despite opiates, the pain remained severe. She also complained of severe back and leg pain. Within two hours, the blood pressure and pulses became unobtainable in the upper extremities. The right femoral pulse also disappeared. Urine output was negligible. Bowel tones were absent and the left lower quadrant developed spasm and rebound.

What's Your Diagnosis? Turn to page 154.

IT'S THE LAW

Freedom of religion does not bar blood transfusions for a child. The supreme court of New Jersey said that the right to practice religion freely does not include liberty to expose the child to ill health or death. It held that parents may be free to become martyrs themselves, but they have no right to make martyrs of their children.

State vs. Perricone, 181A, 2D, 751 New Jersey, June 4, 1962
Stetler & Moritz

There's a Difference

Actually there's only a slight difference between keeping your chin up and sticking your neck out, but it's a difference worth knowing.—News, Milford, Mass.

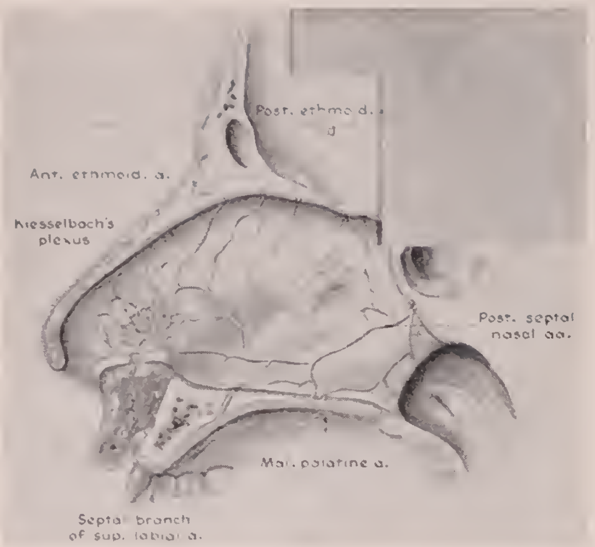

Fig. 1 — Sphenopalatine artery showing septal branch descending on the septum.

Nasal Hemorrhage

THE NOSE is a vulnerable, vascular organ which bleeds easily and troublesomely. Nasal bleeding can result from trauma, but more often occurs spontaneously. The etiology in this latter case becomes apparent only after the flow of blood has been adequately controlled. Bleeding in traumatic cases is rarely as troublesome as in those of spontaneous origin.

Etiology of Nasal Hemorrhage

Upper respiratory infection, resulting in heavy nasal crusting, is the most common cause of erosion of the mucosa and resultant hemorrhage.

Systemic Disease

Underlying systemic disease such as uremia, diabetes mellitus, hypertension, cirrhosis of the liver, and blood dyscrasias, all make bleeding more difficult to control.

Patients often ask if nasal hemorrhage is caused by high blood pressure. The answer is usually no. Nasal hemorrhage starts because of some local pathology, but is of course much more profuse and difficult to control in a patient in whom the blood pressure is elevated. Patients receiving anticoagulant medication for vascular disease naturally have more profuse bleeding if they happen to suffer a nasal hemorrhage.

Local and Paranasal Abnormalities

Local abnormalities of the nasal septum are almost constantly aggravating factors in epistaxis. High fever associated with any acute infection can result in dryness and crusting. Tumors of the nose, paranasal sinuses, and the nasopharynx are all potential sources of nasal bleeding. Nosebleeds can occur at any age but are far more common and much more troublesome in patients of advanced years.

Seasonal Influence

The condition is also seasonal. During some winter months epistaxis seems to approach epidemic proportions, the prevalence of upper respiratory infections and the low humidity of our well-heated homes and offices being the chief causes of this seasonal variation.

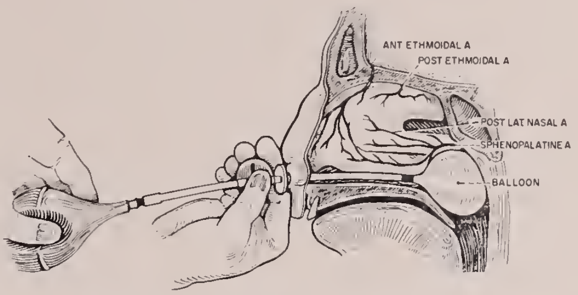

Fig. 4 — Fox postnasal balloon

The Treatment

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Anatomical Considerations

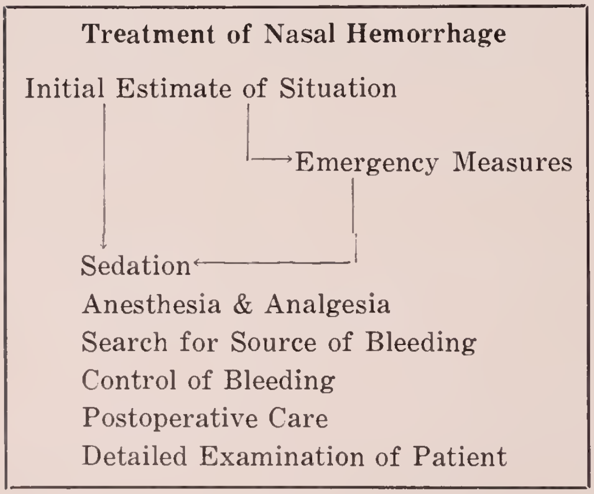
The anatomy of the nose must be understood if proper treatment of nasal hemorrhage is to be achieved. The nose has such an exceedingly abundant blood supply because of its vital function in the conditioning of the inspired air that bleeding can occur from the septum, the floor of the nose, the turbinates, and the lateral wall. The blood supply is received from the external carotid artery and its branches, and from the ethmoidal arteries, branches of the ophthalmic, which in turn is a terminal branch of the internal carotid artery. The ethmoidal arteries supply a relatively small part of the nose (the olfactory area and the superior parts of the septum), but when there is bleeding from this area it can be troublesome, because of the inaccessibility of the bleeding point and of the artery supplying the area. The greater portion of the blood supply to the nose is directly from the external carotid system. The sphenopalatine artery, a terminal branch of the internal maxillary, enters the nasal space through the sphenopalatine foramen and promptly divides to supply the septum and the corresponding lateral nasal structures. Its main septal branch then descends on the septum, as shown in the diagram (Fig. 1), to end in the plexus in the lower anterior portion of the septum known in America as Kiesselbach's area, and in England as Little's area. Here there are anastomotic connections with the anterior ethmoid, the external maxillary, and the greater palatine arteries. Ninety percent (90%) of all nasal hemorrhages originate in this part of the nasal septum. It seems appropriate here to mention that the American surgeon, Dr. James Lawrence Little, published his lucid description of the blood supply of the nasal septum five years before this was done by the German otolaryngologist, Kiesselbach.

If the nasal septum is straight, controlling the bleeding from this structure is usually easy, since pressure can be firmly applied. However, the nasal septum is frequently irregular in shape, and this is especially true in patients prone to have nasal hemorrhage. The turbinates in their normal form are curved, irregular structures; hence bleeding from the lateral wall of the nose is generally more difficult to control, because here it is hard to visualize the bleeding vessel and often difficult to apply firm pressure that should be maintained until the hemorrhage is stopped.

Anxiety and apprehension are constant companions of epistaxis. These emotional factors increase the systolic blood pressure and hence aggravate the bleeding. It is interesting to note that Aretaneus, writing of nasal hemorrhage two thousand years ago, said: "The patient despairs from the first and needs to be strongly reassured." Obviously the human reaction to blood loss has remained unchanged. Sedatives are useful in allaying the patient's apprehension, but they can be greatly potentiated by the physician's calm demeanor and firm assurance that the hemorrhage can and will be controlled. The patient should be told that the safest and simplest procedures will be tried first, but should these fail, stronger and surer measures will be brought into operation promptly.

Control of Nasal Hemorrhage

The following outline in seven steps represents an orderly approach to this problem:



Treatment of Nasal Hemorrhage

Initial Estimate of Situation

Emergency Measures

Sedation

Anesthesia & Analgesia

Search for Source of Bleeding

Control of Bleeding

Postoperative Care

Detailed Examination of Patient

The Estimate of the Patient's Condition

This can be made quickly by observing the patient's color, pulse, and blood pressure. A hemoglobin determination can be made, and if the patient's condition suggests profound blood loss, typing and crossmatching should be done so that blood can be obtained for transfusion. If, in this quick appraisal of the situation, there is evidence of some serious emergency such as shock or obstruction of the airway by massive bleeding, corrective measures must be taken immediately and the actual treatment of the nosebleed given secondary consideration for the moment.

Sedation

This is most important because an anxious patient is much more difficult to treat than one who is relaxed. Moreover, since we anticipate using a topical anesthetic in the nose, it is a wise precaution to have the patient fortified with one of the short acting barbiturates such as pentobarbital or secobarbital. The dosage should be adequate for the patient's age and size, and the medication can be given either orally or parenterally.

Analgesia

Since the nasal mucosa is extremely sensisive, good nasal work cannot be done without relieving the patient of pain. A hypodermic injection of morphine, codeine, meperidine, or some other narcotic should be administered before proceeding to the actual control of the bleeding. Further analgesia can be obtained from application of the topical anesthetic to the nasal mucosa.

Search for the Source of Bleeding

The importance of this is obvious, and the methods will be described in the text to follow.

Control of Bleeding

This is the crux of the discussion. The techniques will be dealt with in detail in the subsequent paragraphs.

Postoperative Care

This pertains to whatever arrangements are made for the care of the patient after controlling the hemorrhage. Secondary bleeding frequently arises from failure to give these matters proper attention.

Detailed Examination of the Patient

An orderly, thorough examination with all necessary tests should be made, once the patient's nasal hemorrhage has been controlled. In this way serious underlying diseases will be discovered and proper therapy can then be instituted.

Control of the Bleeding Point

Now the physician is ready to search for the bleeding point so that he can control the hemorrhage promptly and with a minimum of discomfort to his patient. Unfortunately, it is at this point that many physicians forget general surgical principles, and in a flurry of anxiety, blood, and often tears, attempt to pack the nose without first carefully preparing and inspecting it. The patient with a nosebleed must be in a situation where he is comfortable, where the surgeon has good light and an adequate supply of necessary materials and proper instruments. The accompanying illustration (Figure 3) shows clearly how few instruments and supplies are necessary.

Now with the patient properly prepared and comfortably seated in good light, the nasal space from which the blood is coming must be visualized with the nasal speculum. If necessary, gentle suction can be used to clear the cavity of blood.

Cocaine and Epinephrine

Long strips of cotton or narrow gauze saturated with 10% cocaine hydrochloride mixed with equal parts of epinephrine solution 1:1000 are then placed in the nasal cavity. It is advisable to use a number of such packs so that the entire lining is rendered anesthetic. Epinephrine serves as a quick acting hemostatic. Even though bleeding is coming from only one side of the nose, it is helpful to place some of the anesthetic in the opposite side so that the instrumentation will be less painful to the patient.

Nasopharyngeal Clot

While waiting for the topical anesthetic to have its effect is a good time to examine the mouth and pharynx. Often there are large clots of blood hanging from the nasopharynx and causing the patient considerable discomfort. These can be removed with the suction tip or the long curved forceps. It is also important to note the amount of bleeding occurring postnasally. With the patient sitting upright, if the bleeding point is anterior, there will be very little bleeding into the pharynx. If there is a steady flow of blood posteriorly and the anterior nares are not obstructed, it indicates that the bleeding is from the posterior part of the nasal space.

Chemical Cautery

As soon as the anesthetic packs have been removed the nasal space is quickly and carefully inspected again, using the suction tip if necessary to keep the area free of blood. If the bleeding point can be clearly localized, it should be cauterized promptly with one of the agents mentioned above. A chromic acid bead is very convenient and forms a firm eschar over the bleeding area. It is advisable to concentrate the cautery on the bleeding point; but if there seem to be several prominent vessels surrounding this or leading into this area, it is wise to cauterize the entire region in linear or grid fashion. The purpose

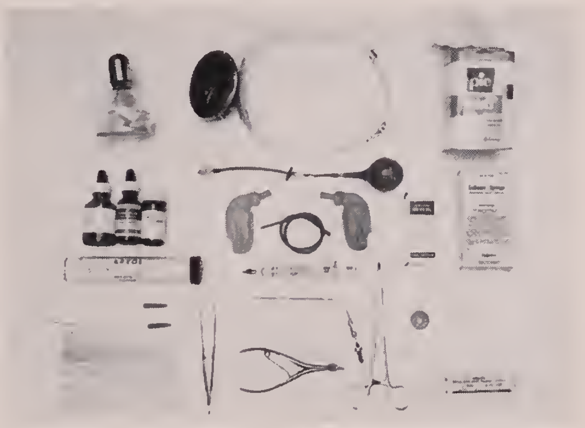


Fig. 3 — Instruments, medical supplies, and medicines (left to right)

1. Alcohol lamp
2. Head mirror or headlight
3. Cotton
4. Cocaine HC — 10%, Epinephrine (topical) 1:1000, chromium triofide crystals, silver nitrate sticks
5. Stevens balloons, Fox balloons, catheter (#10 French), syringe 10.00 cc. and hypodermic needle (25 gauge)
6. Oxycel (cotton and gauze), gelfoam and silk thread (#2)
7. Metal applicators, tongue blades. long curved forceps
8. Nasal speculum, bayonet forceps, suction tip (#8 French)
9. Half-inch lubricated packing (vaseline and adaptic) and gauze squares (2" x 2")

of this is to allow for some normal mucosa to remain to epithelialize the cauterized area as healing develops. Silver nitrate in the form of a stick can be used in exactly the same manner, but it does not produce quite as prompt a cauterizing effect. Trichlorocetic acid can be used, but because it is a liquid there is more likelihood of its running down onto the patient's face and causing some cutaneous burns. Prior to using any of these chemical cauteries it is advisable to apply a little petrolatum or other mild ointment to the nasal vestibule to protect the skin from the corrosive chemicals. Electrocautery can be used effectively but is somewhat more painful if anesthesia is not complete; it also has the disadvantage of tending to produce an adherent crust which can be pulled away as the instrument is withdrawn, thus reopening the cauterized vessel. Chemical cauteries do not have this disadvantage.

Nasal Packing

Once the hemorrhage is stopped, the area can be firmly packed with petrolatum gauze, or Oxycel, Surgicel, or Gelfoam. At times the bleeding is so brisk that it is impossible to dry the field sufficiently so that cauterizing agents will work. In such a situation it is necessary to apply firm pressure with epinephrine packs and maintain this pressure for several minutes until the bleeding has stopped or at least slowed enough so that the cauterizing agents can be used effectively. If the bleeding is localized and has been promply controlled, there is no need to pack the nose completely. Some packing should be placed directly over the cauterized area in such a position that firm pressure will be maintained. In this way it is often possible to leave the patient's airway unobstructed. If the packing has to be done without any attempt at localization of the bleeding point, or if the bleeding point cannot be found on careful search, the surgeon is forced to pack the entire side of the nose. To do this properly the nose must be well anesthetized and a continuous strip of suitable ointment-coated gauze placed in the nose.

Method of Packing

The packing can be started either on the floor of the nose or high up in the middle and superior meati. It must be placed firmly but carefully in the nose, layer on layer, until the entire space is packed. Unless the nose is prepared with topical anesthesia and vasoconstriction, it is very difficult to see into the back of the cavity and to place the packing well under and around the turbinates. Failure to place the pack far enough back is often the cause of continued bleeding. If the packing can be placed accurately according to the anatomical structures, great force is never necessary. If there is a sharp angulation of the nasal septum producing a deep concavity in which the bleeding is arising, adequate pressure often cannot be applied to the bleeding point. Therefore it is always preferable to localize the bleeding point if possible and place the pack directly against it.

Ointment-Impregnated Gauze

Narrow, ointment-impregnated gauze is almost always available and is an excellent material for packing the nose in this fashion. Dry gauze should be avoided except in emergencies, because of the tendency for secretions to fill its meshes and to dry and adhere to the delicate mucosa.

The Postnasal Pack

Postnasal packing is a technique which every student in medical school is taught, and almost every physician, early in his practice, is eager to try. On gaining more experience with the use of this procedure, most physicians tend to use it less freely. It is generally very painful for the patient and is fraught with many possible complications. Therefore it should be reserved for the true emergency situation. The postnasal packing, if possible, should be fashioned so it will fit snugly into one choana and not be a large bulky mass of gauze which partially or almost completely fills the nasopharynx. It must be remembered that postnasal packs serve two functions: (1) to exert pressure against the bleeding sphenopalatine artery or other postnasal vessel; (2) to provide firm posterior occlusion of the nose so that the anterior packing can be applied and maintained at an effective pressure against some inaccessible bleeding point.

Hallberg's Method

Hallberg's method of preparing a postnasal tampon from a small gauze square is an excellent one. It is advisable to saturate the pack with some antibiotic ointment such as bacitracin, because in cases requiring postnasal packing, it is usually necessary to leave the pack in place for several days.

It is also essential that some sort of "pull-out" string be left in place. Usually it is not necessary to bring the string out of the mouth and tape it to the cheek; the thread can be cut off at the level of the tip of the uvula where it can be reached at the time of removal. If the postnasal packing in itself stops the bleeding promptly, then additional anterior packing is unnecessary.

Complications

The complications of a postnasal pack are chiefly related to the ear. The oversized improperly fashioned postnasal tampon lies exceedingly close to or over the orifice of the Eustachian tube, and many patients with nasal hemorrhage treated in this way will develop an acute otitis media. Cases of fatal meningitis have even been reported from the improper use of postnasal packing, which too often is placed with more force than is actually necessary. In this way the delicate underlying mucosa is contused and abraded and can eventually become necrotic.

The Fox Postnasal Balloon

Postnasal packing can be accomplished less traumatically with the use of balloons. The one illustrated in Figure 4 is called the Fox postnasal balloon. Its function is exactly the same as the postnasal pack; it is either to exert direct pressure on posterior bleeding points or to occlude the choana so that the anterior packing will be more effective. As can be seen, the balloon is mounted on a small catheter, which can be inserted through the nose, preferably under direct vision; then, when it is in place in the nasopharynx, a small rubber syringe is applied and the balloon is inflated. The catheter is then drawn forward until the balloon fills the choana firmly. This placement of the Fox balloon must be accomplished either under visual or digital control.

The balloon is extremely distensible and if overinflated will fill the entire nasopharynx and oropharynx. If it is too small, it will fail in its mission of applying pressure and occluding the posterior choana. Once the balloon is in proper place it can be anchored by means of a rubber disc which is part of the apparatus. Prior to this final adjustment, the anterior packing, if necessary, is placed. This device is much less uncomfortable for the patient than the postnasal tampon; but it is not without its hazards. What seems to be gentle pressure from a very soft balloon can be damaging if exerted over a long period of time. The tissues around the posterior choana frequently appear quite inflamed when visualized after removal of such a balloon. Because postnasal packing of whatever sort is uncomfortable, it is almost mandatory that a patient so treated be hospitalized, in order to obtain sedation and analgesia as required.

Stevens Balloon

The other kind of nasal balloon illustrated in Figure 3 is called the Stevens'. It is of molded rubber design to conform to the irregular contours of the lateral nasal wall as created by the turbinates; in other words, it is one of a pair of balloons, a right and a left. This set of intranasal balloons is to replace gauze or cellulose or gelatine packing. Because it is a mechanical device does not mean that it is simpler to use than ordinary packing; in fact, it is probably more difficult to use properly than packing materials placed with the bayonet forceps.

The Stevens' balloon for the bleeding side is selected and first tested to see that there are no air leaks.

It is then completely deflated, lightly lubricated with antibiotic ointment, grasped carefully with the bayonet forceps and placed along the floor of the nose. There is a strong tendency for it to catch on the deviations of the septum and to roll up as it strikes the turbinates. Therefore, it must be placed under visual guidance after inserting it far back in the inferior meatus; then it is unrolled and flattened out against the septum, bringing its superior border as high as possible in the nasal vault. When this has been accomplished, air is pumped into the balloon by means of a small hypodermic syringe, the amount required depending on the size of the nose and the severity of the nasal hemorrhage. When the balloon is in proper place, the inflating end should be well outside the anterior naris. If only one side is being treated with the Stevens' balloon it is essential that the balloon be fixed to the patient's face with adhesive tape. This is accomplished by tying a silk thread or a piece of string around the neck of the balloon and taping it in position. If bilateral packing with Stevens' balloons is being done, the two balloons can be held together anteriorly with a rubber binder. Again, the pneumatic pressure of a soft balloon is not painless and is not entirely harmless. The patient with a severe nasal hemorrhage which has been controlled with a Stevens' balloon well inflated, is usually so uncomfortable that he will require hypodermic analgesia. Therefore, in treating patients with such a device it is well to hospitalize them.

After Care

All patients who have undergone such treatment, if ambulatory and allowed to go home, must be warned of the danger of recurrent hemorrhage and against any manual manipulation of the nose for one week. They are also told that no physical activity of a strenuous sort should be indulged in for at least that period of time. If the bleeding can be controlled for a week, usually the eschar is firmly attached and healing is progressing well enough so that there is very little danger of recurrence. If brisk bleeding recurs, the initial procedure must be repeated.

Ligation of Vascular Supply

If all attempts have proved futile and bleeding persists, it is best not to temporize but to proceed toward the final step which is ligation of the main artery supplying the bleeding area.

Ethmoid Vessels

If bleeding is known to be high in the nose anteriorly, it can be concluded that its source is from the ethmoidal vessel. The anterior ethmoidal artery can be ligated through a curved incision under the medial portion of the eyebrow. This is a procedure, however, which should not be attempted by anyone who has not had experience operating in this special area.

External Carotid Artery

The majority of nosebleeds are not from the ethmoidal circulation, but are in the area supplied by the external carotid and its branches; therefore, in these cases positive control of the hemorrhage can be obtained by ligation of the external carotid artery.

Carotid ligation is a major procedure but one which can well be done by anyone with general surgical training and proper knowledge of the anatomy of the neck. It is essential that the surgeon remember that ligation of the external carotid is, in a sense, a temporary measure. The nasal hemorrhage will stop promptly with ligation, but collateral circulation will be established in a few days and theoretically bleeding can recur and sometimes does. There have been cases reported in which both external carotid arteries have been ligated without ill effect. The patient tolerates this type of surgery very well, and it can be performed nicely under local anesthesia. If the patient's condition is satisfactory, there is no reason for avoiding general anesthesia. However, the surgery must be done carefully with good hemostasis so that vital structures are not injured.

Summary

Nasal hemorrhage can be a serious and trying problem. The physician must make a prompt estimate of the general situation and take proper steps to correct the abnormalities. The patient must be reassured and given proper sedation and analgesia. The nasal spaces must be carefully examined and the type of bleeding diagnosed. If a tumor is recognized or suspected, temporary measures must be taken to control the bleeding so that the patient can be placed in the hands of someone capable of removing or caring for the intranasal lesion. The vast majority of nasal hemorrhages are simply eroded blood vessels that require control. Ninety percent arise from the lower anterior part of the nasal septum, designated as Little's Area. With proper light, analgesia and anesthesia, most of such bleeding vessels can be localized and treated. Control is usually accomplished by means of cauterization and application of sufficient pressure by means of packing or special nasal balloons so that further bleeding does not recur. The postoperative treatment is very important, because it is during this period that the previously bleeding areas must heal. It is also during this time that the patient's general condition should be studied, so that any underlying causative factors can be discovered. If local deformities in the nasal septum have added to the problem of control of the nasal hemorrhage, plans should be made for corrective surgery.

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PATRON SAINT FOR FEBRUARY

St. Blaise

February 3 commemorates St. Blaise, another of those rare characters like St. Didacus, whose indefinably human appeal and magnetism distance cannot dim. His story is brief and simple but touches the heart warmly as we read it.

An Armenian monk of the 4th century, Blaise devoted himself to medicine to the exclusion of all else except prayer. To escape persecution for his Christian commitments and to minister to the sick he retired to a mountain cave, where he could pray undisturbed and whither multitudes of ill and injured humans and animals flocked to be cured. Legend has it that through some sort of sixth sense the animals, no matter how dire their need, never disturbed their benefactor at his prayers but waited patiently and silently until he had concluded.

It was on such an occasion, when a large group of animals — wolves, bears, lions, tigers — were assembled near Blaise's cave waiting for him to finish praying that their presence in a body was noted by the agents of Agricola, Governor of Cappadocia, who happened to be patrolling the area; thus Blaise's presence was detected and he was promptly arrested, to be thrown into a lake to drown. But instead of sinking he stood and walked on the water, suggesting that his persecutors do likewise. Attempting the feat in order to capture him, they all drowned.

While Blaise remained on the surface, unaccessible and triumphant, an angel voice urged him to return to dry land to meet his inevitable martyrdom. He did so and was beheaded.

Blaise is the saint effective against throat disorders and diseases, as legend has it that he once extracted a fishbone from the throat of a child who would otherwise have choked to death.

To avoid trouble, breathe through the nose. It keeps the mouth shut.

— Woodmen of the World

The Treatment

ACROMEGALY WAS first described by Pierre Marie.[1] Classic signs and symptoms have been outlined by Davidoff.[2] Decisions regarding the necessity for treatment are usually made on the basis of such findings. Initial therapy is generally X ray unless a neurosurgical emergency is evident. In many patients insidious endocrine changes continue in spite of the usual dosage of radiation therapy. Continued soft-tissue swelling, increasing size of acral parts, diabetes, increased perspiration as evidence of hypermetabolism, arthritic symptoms, and at times congestive failure, without other specific cause, indicate most probably growth hormone activity even without eye signs or headache. A radio-immunoelectrophoretic assay of growth hormone has been reported, with good differentiation of acromegalic patients from normals;[3] however, this assay is not yet clinically available and determinations of activity in acromegaly have to be made without it.

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*Experience at the University of Minnesota Hospitals and the Minneapolis Veterans Administration Hospital from 1940 to 1963.

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# of Acromegaly*

In a recent series of 101 cases, 48% died before age 50,[4] about one half of the deaths being due to cardiovascular causes.

For these reasons investigators have been looking for other methods of therapy, one of which involves the use of high doses of estrogen to produce suppression of pituitary function.[5] Also the advantages of heavy alpha particle radiation therapy have recently received increased impetus,[6] and total hypophysectomy as initial treatment has been advanced with more vigor.[7] It still remains difficult, however, to decide which form of treatment to use when faced with the individual patient with active acromegaly.[7-9] With this thought in mind, particularly in relation to initial therapy, the records of patients with acromegaly at the University of Minnesota Hospitals and the Minneapolis Veterans Administration Hospital were reviewed, with the hope that some clues to more adequate therapy, especially of the endocrine aspects of the disease, might be uncovered.

Clinical Material and Methods

The case records of thirty-five patients with acromegaly active enough to have some form of initial treatment were reviewed. This represented essentially all patients with documented acromegaly in whom records were sufficient to evaluate the initial therapy. The study included some seen only on the neurosurgical or neurological service, some primarily evaluated and followed by the radiology department, and some seen mainly for metabolic or endocrine complaints. The admittedly rather crude criterion of success or failure was to note whether any subsequent treatment became necessary.

An attempt was made to evaluate the severity of the disease at the time of initial treatment. Each of the following six parameters was given one point if present:

1. Progressive acral enlargement
2. Recent onset or exacerbation of diabetes
3. Elevation of serum phosphorus
4. Progressive loss of visual fields
5. Persistent or progressive headaches
6. Sella enlargement

The most "severe" acromegalic patient would then have a "score" of six points. The reasons for retreatment were classified as:

a. "Neurologic"
b. "Endocrine"
c. Both

"Neurologic" causes included the last three parameters listed above. If the reason for retreatment centered mainly on the first three symptoms, the cause was classified as "Endocrine." In deciding in which category to place patients requiring retreatment, certain other factors of an insidious nature such as skin thickening or puffiness, increased perspiration, progressive weakness and fatigue, helped to influence the decision toward "Endocrine" causes. These were considered only when they were specifically recorded on the chart.

Radiation dosages ranged from 2,000 to 4,000 tissue roentgens. Hypophysectomies were done by the transfrontal craniotomy approach.

Results

The types of therapy, divided into three categories, are outlined in Table 1.

TABLE 1

Types of Initial Treatment of Acromegaly

Radiation only	27
Surgery + immediate radiation	6
Surgery only	2
	35

Hypophysectomy Only

The two patients with hypophysectomies only, underwent surgery in 1962 and had only three and eleven months of followup, respectively. Neither required further treatment during that time.

Radiation Only

The results of initial radiation only are presented in Table 2.

TABLE 2

Results of Patients Treated with Radiation Only

16	No retreatment (0-210 months) (Average 67 months)	59%
9	Further radiation (6-290 months) (Average 79.6 months)	33%
2	Further treatment by surgery (13-36 months) (Average 24.5 months)	8%
Total 27		100%

Thus, 41% of the patients with acromegaly for whom radiation alone was the initial treatment required some form of further therapy.

Surgery and Radiation

The patients subjected to surgery followed by immediate radiation and the two patients subjected to initial hypophysectomy are summarized in Table 3.

TABLE 3

Results in Patients with Acromegaly Treated with Surgery Followed by Immediate Radiation (six), and those Treated with Surgery Only (two)

7	No retreatment (16-186 months) (Average 104 months)	87%
1	Further radiation therapy (after 25 months)	13%
Total 8		100%

The patient requiring further radiation after initial surgery and X-ray treatment had a functioning chromophobe adenoma microscopically. He received 2,880 tissue roentgens in 29 days postoperatively. Two years later, another course of 3,000 tissue roentgens was felt necessary because of increased shoe size, weakness, and fatigue. His serum phosphorus was 5.3 mg./100 ml. and was again definitely elevated. The previous problem of severe headaches and visual field defects was not now present.

Although the number of patients in the surgical category is small, further definitive treatment was necessary in only one or 13% of this group of patients with acromegaly. The reason for the further treatment was considered to be "Endocrine," since there were no further headaches, progressive visual field encroachment, or further sella enlargement.

Severity of the Disease

The comparative "severity" of the disease, according to the methods outlined, and the presence or absence of visual field signs are presented in Table 4.

TABLE 4

Evaluation of Severity and Eye Signs in Patients with Acromegaly

Type of Treatment	"Severity Score"	Visual Field Signs Present
Initial X ray only (27 patients)	3.73	38.4%
Initial surgery + X ray (6 patients) and initial surgery only (2 patients)	4.73	100.0%

Although these designations for "severity" are arbitrary, this table would suggest that the patients receiving surgery as part of their first treatment had more of the accepted clinical parameters of activity present than did those who received radiation only. The presence of significant visual field defects is the most frequent unequivocal factor for precipitating surgery in the newly seen, active patient with acromegaly.

Some form of retreatment was necessary in 12 of the 35 patients. The classification as to cause is shown in Table 5.

TABLE 5

Patients with Acromegaly Requiring Further Treatment after Initial Therapy, and Classification as to Principal Type of Continued Symptoms

"Endocrine" causes	8
"Neurological" causes	2
Both	2
Total	12

The criteria for deciding between the various principal symptoms which precipitated retreatment in each patient were outlined previously. Admittedly, in some patients decision was difficult. The two patients classified as needing further therapy for "Neurologic" reasons had progressive headaches, without other evidence of definite further acral enlargement, diabetes, or increased phosphorus. If the eight patients with "Endocrine" causes plus the two patients with "Both" are put in one group 83% or 10 of the 12 patients had significant "Endocrine" or metabolic reasons precipitating their retreatment.

Discussion

Despite the small number of patients with acromegaly evaluated, treated, and followed in the two hospitals over a 23-year period, the results suggest that the group starting with surgery as part of their therapy had better control of "Endocrine" features of their disease. The length of the follow-up also makes conclusions somewhat tenuous in a disease with such a long natural history. However, from the data available, one could find much support for the view that the usual dosages of 2,000 to 4,000 tissue roentgens employed in these patients for the primarily "Endocrine" aspects of active acromegaly are not enough. At times, more than the 2,000-2,500 tissue roentgens actually given was recommended, but was not considered feasible by the radiologist administering the therapy.

Many endocrinologists have had the feeling that their patients with acromegaly were "smoldering" with low grade activity too subtle to define clearly, but which caused gradual progression of grotesque features and insidious cardiovascular complications. The present study indicates that patients with deep X-ray therapy alone frequently had to be retreated because of suspicious clinical findings. However, patients treated with surgery did not have this same incidence of further therapy. It is, therefore, possible that early surgery should be performed in more cases of acromegaly than is now being done. The younger patients with definite activity would seem to merit particular consideration in this regard.

Summary

The most effective initial treatment in active acromegaly remains undecided when applying it to the individual patient. Thirty-five patients received from 2,000 to 4,000 tissue roentgens as the only initial therapy, of which 41% needed further treatment. One, or only 13% of eight patients who had hypophysectomy followed by immediate radiation, or hypophysectomy alone, required further definitive therapy. The number of patients is small, and the follow-up is relatively short for a disease with a known long natural history. Control of "Endocrine" features of the disease, especially in younger patients, may be better when surgery is part of the initial therapy. Further, well-organized study of surgery versus radiation therapy as initial treatment in acromegaly seems indicated.

Acknowledgement

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The Famous Dr. Jebb

Sir Richard Jebb was a liberal eater, a high liver. He believed the digestive organs were made to be used, not nursed. The question frequently asked by his patients, "What may I eat, doctor?" was exceedingly annoying to him. On one occasion he gave this answer: "My directions, sir, are simple. You must not eat the poker, shovel, or tongs, for they are hard of digestion; nor the bellows, for they will produce wind in your stomach; but you may eat anything else you please."

Oliver Wendell Holmes

Before Holmes was a writer, he practiced medicine, and taught anatomy at Harvard and Dartmouth. As a practitioner he was not successful, for people were a bit doubtful about the flippant youth, who posted the following sign above his office door: "Small fevers gratefully received."

ANSWER TO WHAT'S YOUR DIAGNOSIS

(From page 141)

Dissecting aneurysm aorta with secondary involvement of renal arteries, celiac axis, inferior mesenteric artery, and peripheral vessels.

Do not do unto others as you would that they should do unto you. Their tastes may not be the same.—George Bernard Shaw

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Oral Cytology

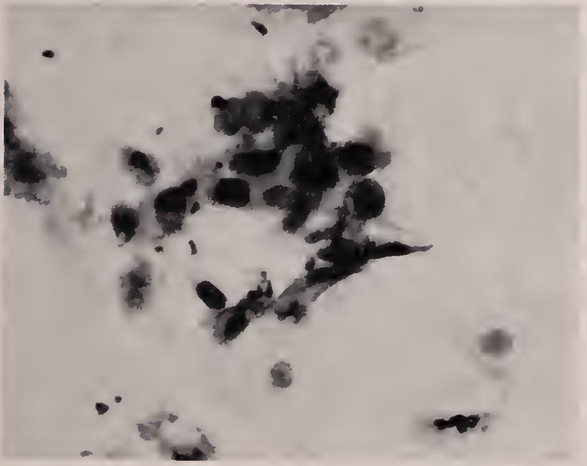

Fig. 1 — Photomicrograph of oral smear (Case 1) (X 530).

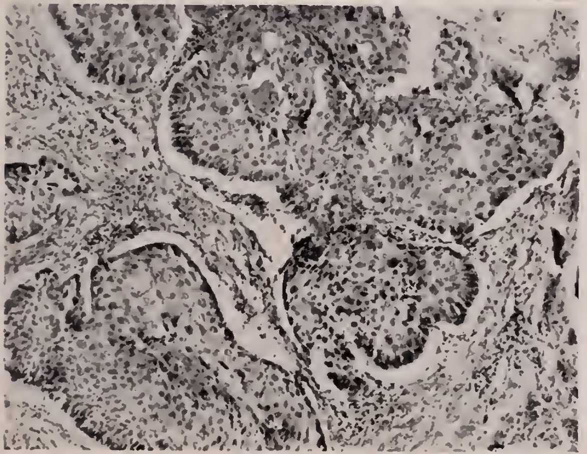

Fig. 2 — Photomicrograph of the biopsy (Case 1) showing squamous cell carcinoma (X 350).

CANCER OF the mouth and pharyngeal mucosa comprise 4% of all cancers in the United States. This group of malignancies cause approximately 4,000 deaths yearly. The death rate is about 75% of the death rate for cervical cancer and about 55% of the death rate for cancer of the rectum. Nearly as many people die from oral cancer as from being hit by an automobile.[1] If one includes carcinoma of the lip, there are approximately forty thousand new cases every year in the United States. Oral carcinoma primarily involves men past the age of forty, the average age at diagnosis being sixty years. The incidence of oral cancer in men is approximately four times that in women, but this ratio is now decreasing. By 1970 there will be nineteen million people in the United States over the age of sixty-five. Consequently with the increasing number in the cancer age group the number of oral cancers will increase markedly.

Sociological Considerations

One must also consider the impact of this disease on the victim. Treatment for advanced cancer is often mutilating. One can hide the scars of most other cancers so that only the patient or immediate family will see them. However, defects caused by the extensive treatment of oral cancers cannot be hidden. Sometimes the patient is reduced to sitting at home, avoided even by his relatives.

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*Pathologist, Rex Hospital,

Early Recognition

It has been estimated that as high as 80% of deaths caused by cancer of the mouth could be prevented by early recognition. These lesions are very similar to the epidermoid lesions of the uterine cervix. Many studies have indicated that they probably all pass through a curable stage. These stages are: (1) Hyperplasia, (2) Dysplasia, (3) Carcinoma in situ, (4) Invasive carcinoma, (5) Carcinoma with metastases.

The duration of each stage is dependent upon many different factors, such as oral hygiene, properly fitting dentures, malocclusion, intercurrent infection, diet, cirrhosis of the liver, and most important, the excessive use of alcohol and tobacco.

The Oral Mucosa

Cancerization of the oral mucosa tends to be multicentric and predisposes to multicentric carcinomas. After one carcinoma of the oral cavity the chance of developing another is ten times greater than in the random population. However, the mortality rate of 75% for carcinoma of the mouth keeps the recurrence rate to a minimum.

Squamous cell carcinoma is by far the most common malignant lesion of the oral cavity and constitutes 95% of all mouth cancers. The other 5% are adenocarcinomas and sarcomas. Thus for practical purposes when we discuss cancer of the mouth we are discussing squamous cell carcinoma of the oral mucosa that arises from a dysplastic process and is present as a carcinoma in situ for a significant period of time.

Cytology Versus Biopsy

Early studies on the cytological examination of the oral cavity were rather disappointing.[2,3,4] However, a study involving 58,497 patients was recently published.[5] This was done by Dr. Henry C. Sandler of the Brooklyn Veterans Hospital. Cytologic examination in this group demonstrated 208 carcinomas, of which 51, or 24.5%, were clinically unsuspected. The clinical appearance of the lesions proved to be an unreliable basis for the diagnosis of early mouth cancer. Numerous other studies have demonstrated that clinical features allow the recognition of advanced lesions only where the prognosis is already poor.[6,7,8]

Diagnosis Early

The importance of early diagnosis of carcinoma of the mouth is indicated in a study by Monaco in a series of 167 cases of cancer of the anterior two thirds of the tongue.[9] He demonstrated that if the lesion was less than 1 cm. in diameter, the five-year-cure rate was 92%. If the lesion was greater than 3 cm. in diameter, the five-year-cure rate was only 17%. The overall cure rate for carcinoma of the mouth and pharynx is approximately 25 to 30%, indicating that these lesions are being diagnosed only when they have already reached the invasive stage. A recent paper from Memorial Hospital in New York covering 1,554 cases of carcinoma of the tongue indicated that before 1940 the overall cure rate was 25% and after 1940 the five-year-cure rate was 35%.[10]

There are three reasons why carcinoma of the mouth is usually diagnosed only in the advanced stages. First, this malignant process is generally asymptomatic. There is rarely bleeding or pain even in the most advanced cases.[11] Second, even if symptoms are present the patient will usually procrastinate and not see his physician or dentist until all home remedies have been exhausted. Third, when the patient finally does arrive at his doctor's office, the lesion is usually treated with antibiotic troches or gargles, or with the topical application of silver nitrate, all this only resulting in further delay. There is probably no other area in the body of comparable volume or easy accessibility that is so neglected as the oral cavity. Many different specialties are involved with this area, but because of the complexity and the conflicting interest of these specialties serious disease is sometimes not diagnosed. The individual specialist tends to examine only the area of his specific interest. Thus, the family physician looks at the tonsils, the dentist examines the teeth, the otologist peeks in the ear, the internist looks at the tongue, and the general surgeon palpates at the thyroid gland. Very few look at the oral mucosa. Almost no one biopsies lesions of the oral cavity.

Biopsy

There are many problems associated with surgical biopsies of oral lesions. The process is time-consuming, somewhat expensive, uncomfortable for the patient, and often technically difficult for the physician or dentist. Also multiple biopsies are frequently necessary; consequently the lesions of the oral cavity are not biopsied. The lesion is often treated with silver nitrate in the fervent hope that it will disappear. Consequently the doctor gambles statistically with watchful waiting, and if the lesion disappears, carcinoma is usually ruled out. However, about one out of every forty of these lesions is a malignancy, and delay allows a treatable lesion to advance to a point where only palliation is possible.

In numerous large series it has been demonstrated that oral cytology and biopsy are about equally reliable.[12,13,14] There are many advantages to the cytologic evaluation of lesions of the oral cavity. The procedure is simple, painless, and inexpensive. Properly prepared scrapings are stained with the routine pap stain and the examination is relatively simple. There are no endometrial or endocervical cells to confuse the cytologist; macrophages are rare. A suspicious smear must be followed by a biopsy, for under no circumstances can definitive therapy be given on the basis of a smear.

Clinical Manifestations

Early carcinomas of the mouth may assume various clinical manifestations. For the most part, any lesion of the mouth that appears different from the surrounding mucosa should be cytologically examined. Carcinomas of the mouth initially have a granular texture, and there is often erythema of the surrounding mucosa. The tumor area is usually lighter in color than the surrounding mucosa and often raised and indurated: the classic appearance of early carcinoma of the mouth. Unfortunately, however, early carcinoma of the mouth can take on any appearance.

White Patch

Leukoplakia is a very unfortunate term. It was coined by Schwimmer in 1877 and is a gross description meaning white patch. Thus, lichen planus, any of the hereditary dyskeratoses, benign hyperplasia, or premalignant lesions are all called leukoplakia. If we remember that leukoplakia simply means white patch and restrict it to a gross description, much confusion is eliminated. Histologically a lesion of the mouth should be given a descriptive diagnosis to differentiate premalignant from benign conditions.

Location of Lesions

The mucosa of the entire oral cavity is susceptible to the development of carcinoma. The locations and incidences of squamous cell carcinoma of the mouth are as follows:

Soft palate —14%
Alveolar ridge —13%
Oral pharynx —10%
Buccal mucosa —8%
Floor of the mouth and tongue —47%
Other —8%

Needless to say, all of these areas can be very readily examined and palpated, and smears made.

Oral cytology is also a very valuable method for following treated carcinomas of the mouth. Atypical cells appear on the smears before the clinical lesion is noted. By following the oral cavity with the oral pap smear, definitive therapy can be given much sooner for recurrent lesions.

Procedure for Cytologic Examination

These smears should be sent to local pathologists for cytologic evaluation. It is only by this procedure that adequate follow-up and control can be expected. A negative smear does not rule out carcinoma of the mouth; a positive smear does not establish a diagnosis of carcinoma of the mouth. A suspicious smear must be followed by a biopsy. The clinical appearance, the history, the age of the patient and various other factors must be correlated. This can be done only by the individual attention and co-operation of the pathologist and clinician.

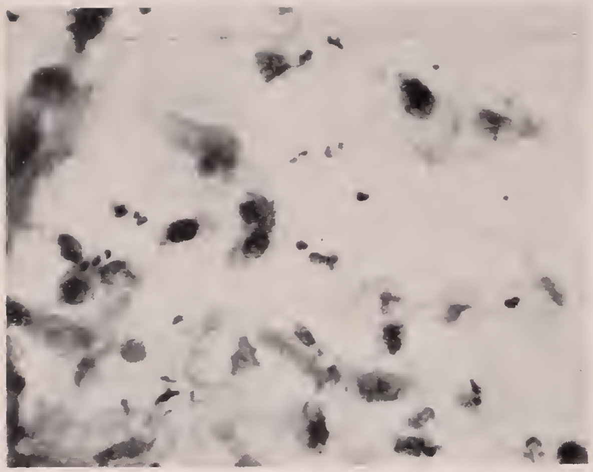

Fig. 3 — Photomicrograph of the oral smear (Case 2) (X 530).

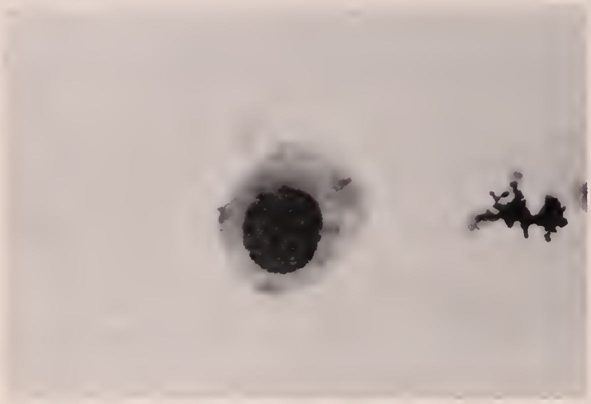

Fig. 4 — Photomicrograph (Case 3) of the smear showing carcinoma in situ cell. (X 980).

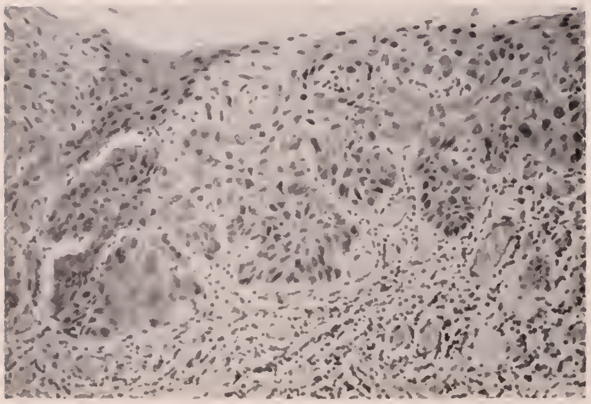

Fig. 5 — Photomicrograph of biopsy (Case 3) demonstrating carcinoma in situ with questionable invasion. (X 400).

Case Histories

During the past three years a program was followed to ascertain if the oral pap smear performed in the private physician's or dentist's office would be a valid procedure for the early detection of carcinoma of the mouth, the smears being sent only to the private pathologist. Previously all the information on oral pap smears had originated from large institutions. This program consisted of presentation seminars for the local physicians and dentists, to acquaint them with the advantages of the smears and to demonstrate the techniques. Supplies, including fixatives and mailing containers, were passed out to the doctors requesting material. The following four cases are representative of the lesions detected by the oral pap smear: lesions that would otherwise have been missed.

Case No. 1.

This 42-year-old woman went to her local dentist because of an infection around a tooth remnant and was referred to a local physician, who in turn referred her to an oral surgeon. All three doctors carefully examined the lesion, and it was their impression that it was benign. Antibiotics were given and a pap smear taken at the same time. X rays demonstrated changes consistent with an inflammatory process. Examination of the smear revealed malignant cells (Fig. 1). A biopsy was immediately performed and demonstrated squamous cell carcinoma (Fig. 2).

Case No. 2.

This 51-year-old white male developed on the glossal pharyngeal fold a lesion that measured 1.5 x 1 cm. and was firm and pale. The dentist examining the mouth thought the process was benign, but a pap smear was performed (Fig. 3). Examination demonstrated atypical cells. Biopsy confirmed squamous cell carcinoma.

Case No. 3.

This 52-year-old college professor went to his dentist because of tingling in a red spot on the floor of his mouth, first noticed in July of 1962 but thought to be inflammatory. In April of 1963, this appeared as an indurated reddish lesion over the left sublingual gland. A smear demonstrated cancer cells (Fig. 4). A biopsy performed demonstrated in situ squamous cell carcinoma with areas of questionable invasion (Fig. 5).

Case No. 4.

This 72-year-old man went to his physician for his routine check-up. Since 1948 this man had had numerous surgical procedures for white patches in the mouth. The first slides demonstrated papillomatosis; in 1959 dyskeratosis was found. A pap smear demonstrated malignant cells (Fig. 6). Biopsy confirmed the presence of carcinoma (Fig. 7).

These cases illustrate the natural history of the disease.

Technique

Oral pap smears are best performed by using a cement spatula or a tongue blade. Prescraping prophylaxis is not necessary. The smear should be immediately fixed with the routine fixative that is used for cervical smears. The interpretation of the oral pap smear is very simple if one understands the limitations. Various areas of the mouth have various cytologic patterns. Generally speaking the areas of the mouth subjected to the greatest use have the greatest amount of cornification. Consequently the hard palate and the alveolar ridge exhibit mostly acidophilic staining cells.[15] Only smears of the uvula show parabasal cells, and these are uncommon. Occasionally columnar cells are encountered from the respiratory epithelium of the oral pharynx.

Certain inflammatory conditions, such as herpetic ulcers, will exfoliate large, bizarre giant cells that appear malignant. With experience one learns to recognize these patterns.

Mucosal Syndromes

There are four hereditary mucosal syndromes that must be recognized. These lesions have distinctive exfoliative cytology.

Darier-White's Disease

This usually begins in childhood and is characterized by numerous discrete flesh-colored keratotic plaques which form crusted areas on the skin and the oral mucosa. Smears demonstrate numerous parabasal cells with large nuclei and mitotic figures. Also cells containing inclusions are noted, which resemble the corps rounds seen in tissue section.[16]

Hereditary Benign Intraepithelial Dyskeratosis of Witkop

This is a congenital disease involving the oral mucosa and bulbar conjunctiva, which occurs in a triracial islet in and around Halifax County, North Carolina. Permanent blindness may result from vascularization of the cornea. Smears demonstrate a marked cornification and a "cell within a cell pattern."[17]

White Sponge Nevus of Cannon

This disease involves the oral, labial, and vaginal mucosa. Smears demonstrate large, wrinkled, pale-staining eosinophilic cells and the presence of organ-staining circumscribed condensations of the cytoplasm.[16]

Pachyonychia Congenita of Jadassohn and Lewandowsky

These oral lesions are clinically similar to the white sponge nevus. Smears demonstrate eosinophilic inclusion bodies and large wrinkled cells. The changes are nonspecific.[16]

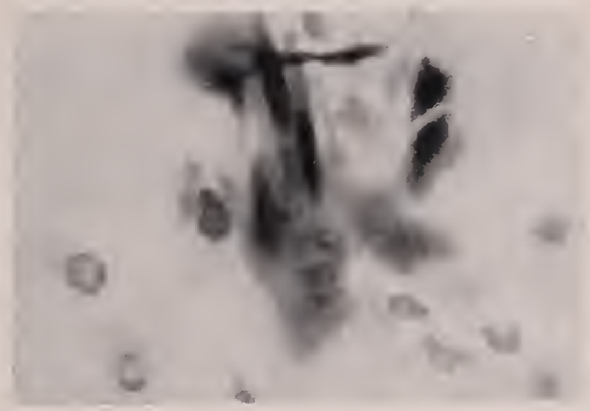

Fig. 6 — Photomicrograph of smear (Case 4) demonstrating spindle cells (X 980).

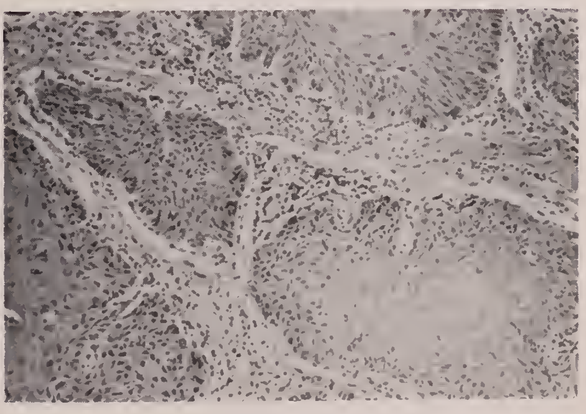

Fig. 7 — Photomicrograph of biopsy (Case 4) demonstrating invasive carcinoma (X 400).

Summary

Oral cytology offers a valuable screening method for the early detection of early carcinoma of the mouth. Its practicality and reliability have been proven. Numerous specific but benign lesions of the mouth may readily be diagnosed by the oral pap smear. A suspicious smear must be followed by a biopsy. Close co-operation of the clinician and the private pathologist is mandatory if this program is to be successful. It is recommended that practicing physicians and dentists routinely examine the soft tissues of the mouth and employ the oral pap smear for the detection of early carcinoma. Only by doing this can we increase the overall cure rate for oral cancers.

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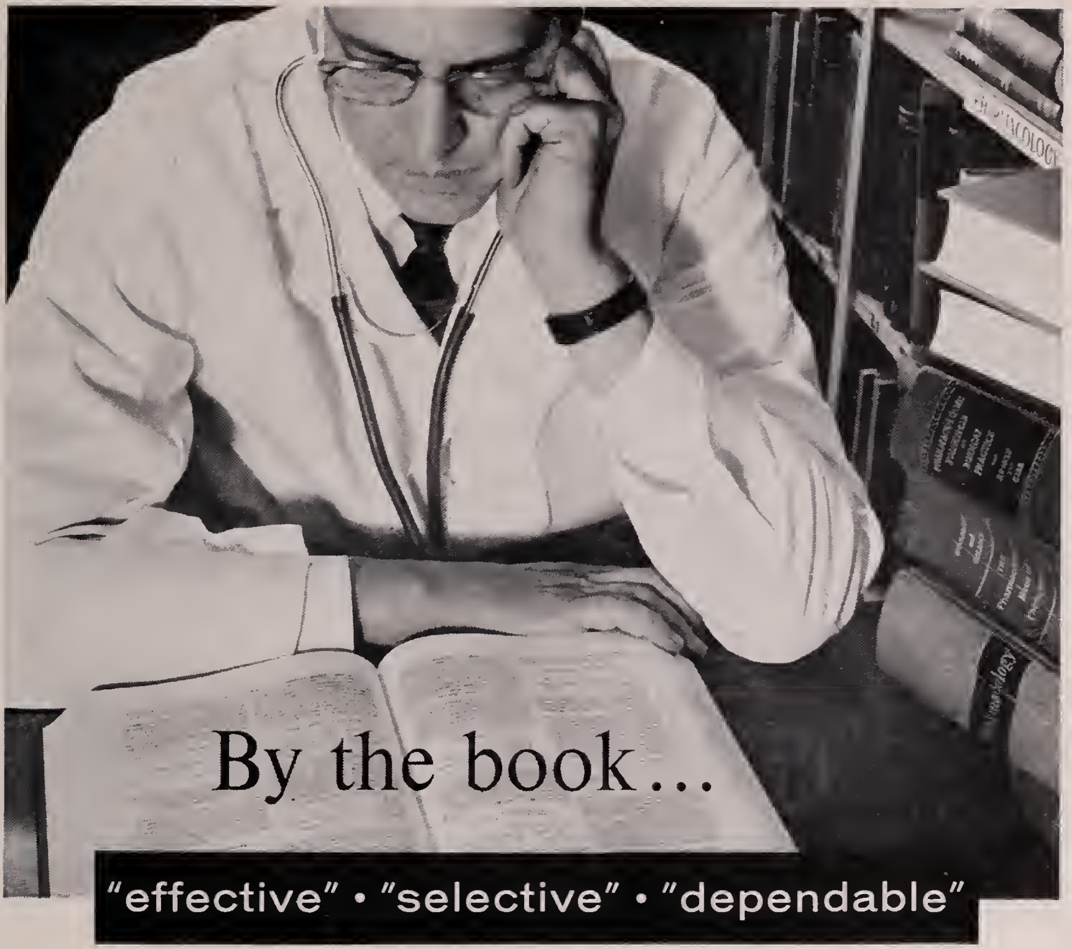
This state of intersexuality is characterized by a female sex chromatin pattern, scanty pubic and axillary hair, underdeveloped labia minora and vagina of near normal depth but ending in a blind pouch. Breast tissue, female habitude and fat deposits are normal. Internal genitalia are absent or hypoplastic. The gonads, consisting of rudimentary testicular tissue without spermatogenesis may be found in the pelvis or the inguinal canals. There is a definite familial tendency. Prognosis for heterosexual adjustment is excellent but sterility is absolute. Other synonyms for this entity are Goldberg-Maxwell syndrome, hereditary male pseudohermaphroditism and Morris syndrome.

The Impossible

Only he who can see the invisible can do the impossible.—Frank Gaines



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Editorials

Patriotism and the Physician

The active physician may not realize how much he contributes to the concept of patriotism; yet, by his daily work, his devotion to patients, and his spontaneous defense of freedom of choice he forges an emphatic contribution to patriotism. He maximizes the freedom of choice to include the choice of hospital, the selection of consultant, and the manner of treatment, insofar as is prudent and feasible.

It should surprise no one, therefore, be he politician, bureaucrat, or autocrat, that the physician is dynamically devoted to freedom. It is the substance of his work and creed. He respects the right of a patient to accept or reject a diagnosis or a proposed treatment. The physician listens, advises, recommends and urges. He abhors coercion and dictation.

Patriotism is neither controversial nor debatable. It is a virtue, based on love and loyalty: a virtue by which we render to our parents and country the honor due: a respect for the Fourth Commandment. After God, we owe to our parents our very being. Parents give life and loving care; the nation gives citizenship and the protection of its laws.

America is unique in history for the love it has shown to strangers. For centuries our land has offered sanctuary to the oppressed of the world. For centuries the liberties enjoyed in America have tugged at the hearts and minds of men everywhere, bringing a floodtide of immigrants pounding at our shores. Small wonder then that we cherish our history and traditions. It is upon this soil and under these skies that, unhampered, we fashion our destiny.

The physician lives close to the body and soul of America. He is loyal to his community, church, school, hospital and other institutions. He does not change location easily, and then only for valid reasons. Fortunately for him, for his patients, and for his country he is not a member of the 'other-directed, lonely crowd,' — the migratory multitudes so ably described by David Reisman. The physician prefers stability. He is close to the parent and child. He knows something about devotion and care.

In all the great wars the physician is to be found, voluntarily, in impressive numbers, at the side of the American soldier. Whether he realizes it or not the ingredients of patriotism are there, bone deep, knowing he must do battle for the cause of freedom.

The physician has nourished freedom since the days of Hippocrates, always seeking the truth about the whole man and how best to help him. Always he views his patient as a human person composed of body and soul: an autono-

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mous individual with an immutable nature, dignified by his own free will and temperament.

So it is that the physician seeks freedom from an oppressive government which dehumanizes his patient; he seeks freedom from the dead hand of a bureaucracy which stultifies the efforts of his profession. All this and much more enters into the concept of patriotism.

S. Francis Ceplecha, M.D.
Redwood Falls, Minn.

On Being Almost Right[**]

LETTERS OF reference commonly make dull reading. When one truly depicts character, the impression is memorable. In such a letter, a retired colonel who headed a military institute recorded his appraisal of a young physician and former student who sought graduate medical training. He said:

> "You have asked my opinion of John Smith who has applied for a fellowship in your program. Apparently in identifying me as one of whom you might request such judgment, he misspelled my name. He never thought such things were important. I did. Signed"

Whether the matter at stake is a referee's name or a patient's life, a certain hazard resides in being *almost* right. To be sure, no one of us is always right. Daily we must decide how much time and effort we will expend to possess that margin which separates the good from the excellent, the right from the almost right. Our choices bear the stamp of our individual tastes and perceptions, and because of those choices, our performances may include some remarkable incongruities. Our manners may be impeccable, but we may be quite insensitive to the demands of proper speech. The average person, William Bean has suggested, is word deaf.[*] "Often he drools words down his chin with wonderfully messy effects that would shock him if words were cereal or a soft-boiled egg." And some stubbornly resist efforts designed to sharpen their grammatic sensibilities. It is far easier to be almost right. Excellence, wherever sought, is not easily found. Its possession requires a mind quick to discernment of flaws, a nature intolerant of needless error, a will unbending in pursuit of high accomplishment.

The traditional toughness of medical school admissions and curriculum standards finds at least partial justification in elimination of some more inclined than others to settle for being almost right. Their elimination, however, is not complete and the consequences of this imperfect elimination range from the predictably disastrous to the superbly amusing. In medical graduate educational programs, for example, each specialty would rid itself of its incompetent trainees by transferring them to some kindred clinical field where, by implication, incompetence is so prevalent and inconsequential that shoddy performance by a new recruit would never be noticed.

But shoddy medical performance can end in disaster for the patient whether the setting of such practices be the diagnostic clinic, the surgical amphitheater, or the hospital bed. Physicians can ill afford to be wrong. Our mistakes may be buried, but in our consciences, they should never be dead. The care of the ill is a rigorous calling: a calling beyond the legitimate grasp of him who would settle too readily for being *almost* right.

Raymond D. Pruitt, M.D.
Chairman, Department of Medicine,
Baylor University College of Medicine

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[*] Bean, W. B.: Tower of Babel 1962. (Editorial) Arch Int Med 110:375, 1962.

[**] Published in Cardiovascular Research Center Bulletin; Vol. 2:2 of Baylor University College of Medicine, Houston, Texas.

How can JOHNSON'S Baby Lotion help the doctor, the mother and the baby?

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The doctor knows the young mother wants to do everything in her power to keep her baby clean and happy and in good health. And more and more evidence points to the fact that the physical expression of her love for her baby is not only a delight to the mother and pleasant for her child, but an essential element in the development of a mature, self-reliant adult.* A father as well as a physician, he knows that Johnson's Baby Lotion not only makes changing diapers easier and more pleasant for all concerned, but that the antibacterial effect of its hexachlorophene content (0.5%) persists for days, to protect the baby's delicate skin from rashes and infections. With Johnson's Baby Lotion normal skin functions are unaltered because the protective film is aqueous rather than occlusively oily. These are some of the reasons so many physicians recommend Johnson's Baby Lotion for routine use to protect delicate skin. May we send you samples of this superior antibacterial emollient in the convenient new plastic bottle?

*Donnelly, J.: A.M.A. Arch. Environmental Health 6:697, June, 1963

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Gastric Freezing for Duodenal Ulcer

ATTEMPTS TO control the duodenal ulcer diathesis have engaged the best efforts of many investigators for several decades. The complexity of the physiologic disarrangement leading to duodenal ulcer can be appreciated from a perusal of the volumes of controversial research and varying clinical responses that have accumulated during recent years.

For most clinicians a reasonable pattern of assessment for a patient's problem has been hammered out over the years at all levels of medical practice. The patient readily controlled on diligent medical management during his initial episode of acute ulceration, and who remains in good health with little difficulty thereafter, presents no serious problem. The patient who goes on to a chronic duodenal ulcer state and experiences a serious sequelae such as severe hemorrhage, pyloric obstruction, perforation, or protracted and disabling pain, has been accepted as a logical candidate for surgery for many years. Recent emphasis upon control of the antral phase of gastric secretion with a hemigastrectomy, coupled with control of the cephalic phase of gastric secretion with a concomitant vagotomy, appears to benefit most patients with complete amelioration of their ulcer diathesis and minimal postoperative sequelae.

The group of duodenal ulcer patients who are more difficult to control, but who are not clear-cut surgical candidates, become chronic problems for many clinicians. Thus, the advent of gastric freezing, aiming to significantly suppress acid peptic secretion without recourse to medications or surgery, has had great initial appeal for patients and physicians alike. The concept of controlling chemical reactivity by lowering temperature is sound and has been well demonstrated to be beneficial in the management of gastric hemorrhage using moderate degrees of hypothermia. Actual "freezing" of the gastric mucosa, however, still appears to be hazardous both in experimental animal studies and in human experience.

Clinical studies from some centers report only temporary relief for duodenal ulcer pain following gastric freezing, and a distressing return of symptoms in a majority of patients within a period of nine months following the freezing procedure. Interestingly, a large number of patients experience a rebound phenomenon of acid peptic secretion following gastric freezing with higher levels found upon testing than existed during the prefreeze evaluation.

At this time, it is the consensus of many investigators that "freezing" of human gastric mucosa to temperatures below zero degrees centigrade commonly leads to necrosis of the tissue and may be dangerous for our patients. However, with further research it may be possible to develop techniques of medication of the tissues involved such that temperatures well below freezing will be safely tolerated. In all probability this research will continue in certain selected centers and future results may bring benefit to many duodenal ulcer patients.

As the problem presents itself today it seems advisable to consider the performance of gastric freezing as a research tool to be used advisedly by highly specialized investigators. The widespread application of this method in community practice appears to be premature at this time.

Claude R. Hitchcock, M.D.
Minneapolis, Minnesota

Letter to the Editor:

The Minneapolis Star published a statement attributed to Dr. Alex Langmuir that the influenza vaccine is worthless. I want to refute that statement.

The influenza vaccine is worthless perhaps when given as directed by the U.S. Public Health Service, but it is of value when given every two months. I began to use this vaccine in 1946 — when I became my own guinea pig and found that if I took it every two months I obtained excellent

Continued

"Upon arising, nose was open" . . . or how another happy patient describes the nasal decongestant action of Dimetapp Extentabs*—how would *your* patients describe it?/ In Sinusitis, Colds, U.R.I., up to 10-12 hours' clear breathing on one tablet/ Also available: Dimetapp Elixir, for t.i.d. or q.i.d. dosage..

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results. I treat many patients and use the Polyvalent A & B vaccine as prepared by many of the pharmaceutical companies.

In 1949 and in 1952 when we had severe epidemics of influenza, I had the opportunity to observe that none of my patients who took the vaccine every two months, came down with the influenza. During these epidemics I treated from 30 to 40 patients daily and in the last two or three years none of my patients who get the injections every two months came down with the influenza. I believe that the influenza vaccine will protect for three or three and a half months, but not for a whole year. Perhaps some day we may have a better vaccine, meanwhile I think an influenza shot every two months is worthwhile.

George Friedell, M.D.
Minneapolis, Minn.

Editor's Note: Oregon Resolution Opposes Food & Drug Administration Ban on Cold Remedies: WHEREAS, the prescribing of antibiotic "cold remedy" combinations by the physician who sees the patient with symptoms of the common cold is a decision to be made by the physician; now

THEREFORE BE IT RESOLVED, that the Oregon State Medical Society does hereby resolve to strongly protest the abrogation of the practicing physician's privilege and duty to prescribe those medicaments which his experience and knowledge indicate to be in the best interests of his patient. — Multnomah Co. (Ore.) Medical Society Bulletin, October 1963.

President's Letter continued from Page 127

discussion charges the Minnesota State Board of Medical Examiners with the responsibility of inspecting schools and hospitals which train applicants for medical examination and licensure in Minnesota. At a special meeting of the Board held on August 30, 1963, it was decided that members of the Board will make personal inspections of the schools and hospitals which they are required to pass upon and which have not already been approved by the former Board of Medical Examiners. Thus all of the five existing schools of osteopathy must be included in the survey.

The inspection is for the purpose of approving or disapproving those institutions on the basis of the opportunity they provide for suitable training for persons desiring to practice medicine under an unrestricted license. This is a difficult and comprehensive project. It is sincerely hoped that the parties involved will co-operate with dispatch and fairness because of the importance of the matter to all concerned. Until the inspection is completed and the training institutions are evaluated, no graduate of a school of osteopathy, unless he is now licensed to practice osteopathy in the state will be eligible for examination here.

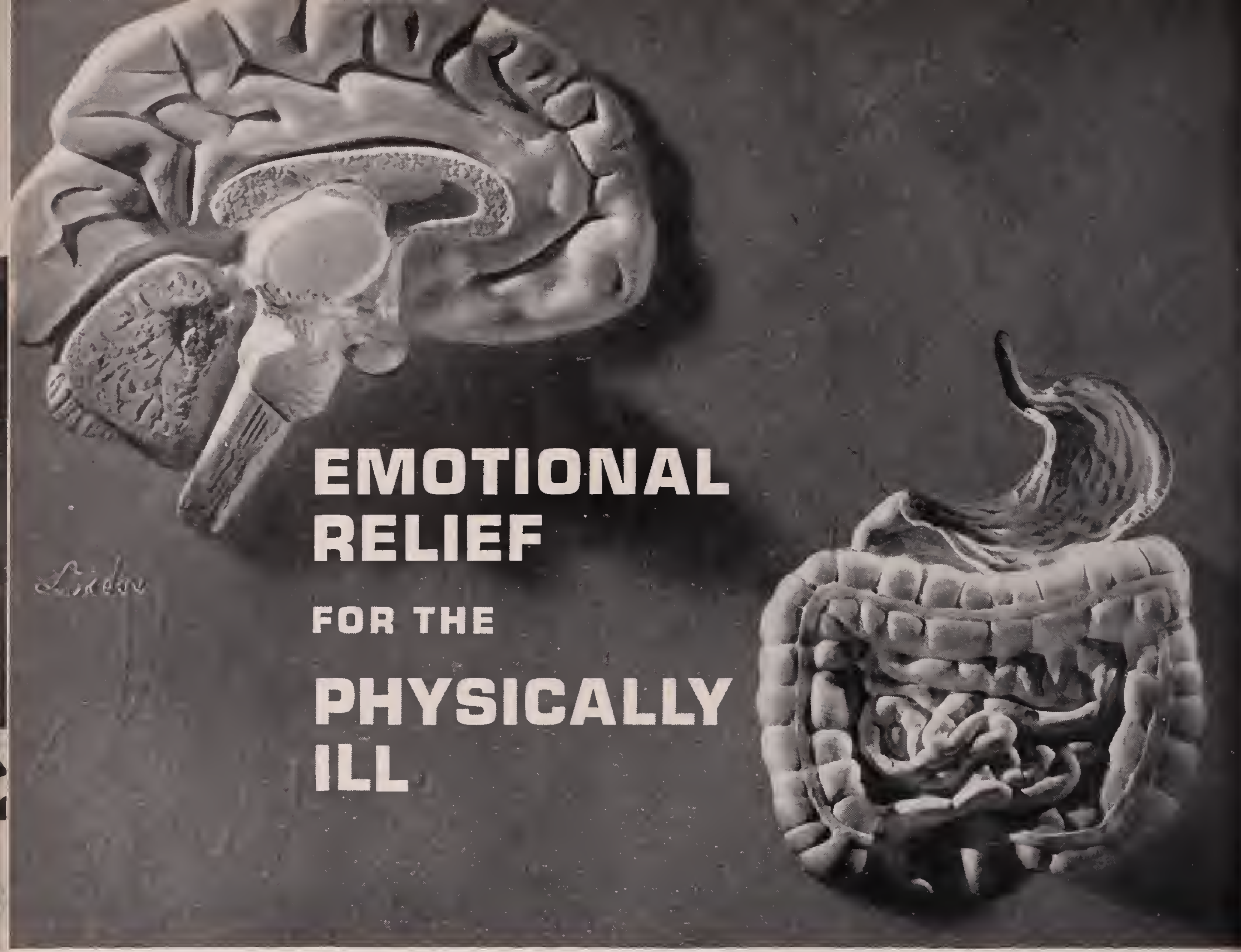
It seems likely that a considerable number of those at present licensed to practice osteopathy in the state will be examined for medical licensure during 1964. The University of Minnesotal Medical School is now conducting a refresher course for these individuals. The course consists of fifty days of lectures and demonstrations spread over a one-year period and it is being well attended by osteopaths from all parts of the state. It is reported by those in charge of the course that they are pleased and actually pleasantly surprised at the knowledge and insight of the registrants.

I hope this brief explanation of the situation as it now stands will be of value.

J. P. Medelman M.D.

John P. Medelman, M.D.
President
Minnesota State Medical Association

False words are not only evil in themselves, but they infect the soul with evil.— Socrates



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Moses the Father of Preventive Medicine

Continued from January issue of Minnesota Medicine

Moses may well be spoken of as the father of preventive medicine. The first five books of the Old Testament, the Torah, are filled with rules and regulations of a medical nature. These rules concerning the preservation of personal and communal health are most fully compiled in the book of Leviticus. While many parts of this book were written after the time of Moses, its basic traditions point back to the great Lawgiver and reveal him as a man deeply concerned with preserving the physical as well as the spiritual well-being of his people. Indeed, the sharp distinction between body and soul was unknown to the ancient Hebrew. To be healthy was to be whole in body and soul together. To this end the Law of God as codified in the Torah gave abundant attention to the preservation of health. The concept of moral holiness contained in the Old Testament laws had implicit in it a style of life for both the individual and the community which was far more successful than that of any of the other great cultures in the ancient world in preventing disease. The code of Moses was a code of social hygiene. There are four kinds of regulations in it which have medical importance.

1. Basic to all Hebrew life was the observation of the Sabbath, a practice enshrined in the Ten Commandments themselves. The legislation about the Sabbath in Ex. 31:13–17 stresses not only religious worship but also physical rest. Freedom from physical effort at regular intervals was enjoined as a means of maintaining physical vigor. It was a regulation which extended not only to men but also to animals. (Ex. 23:12). The body requires regular periods of rest for health. And for reasons difficult to determine, the ratio of one rest day in seven seems uniquely well suited to the full functioning of the human body. The idea of the Sabbath emerges as a prophylactic principle of basic importance for physical and spiritual well-being. It is a principle which can be worthily pondered by those concerned with such problems to this very day.

2. The Hebrews had a complex set of laws regarding edible foods. They drew a sharp distinction between "clean" foods which could be eaten and "unclean" foods that were to be rigorously avoided. The basis for this distinction was not derived from an irrational fetishism but reveals sound insight into hygienic principles. The only animals suitable for food were those that chewed the cud and parted the hoof, since they were exclusively vegetarian. (Lev. 11:3–8 and Deut. 14:4–8). All blood was to be drained from the tissues before cooking; the abdominal viscera were to be avoided, as were all animals that died from natural causes. Among aquatic creatures only those having fins and scales were considered clean. Among birds the rapacious, aquatic and predatory species were rejected. (Lev. 11:13–19).

By using the flesh of only vegetarian animals the Hebrews greatly reduced the probability of infestation by parasites *(Trinchinella spirilis, Taenia solium* or *Echinococcus granulosus)* or the protozoan *Toxoplasma*, all of which are common in carnivora living under sub-tropical conditions. Similarly the exclusion of crustacea which frequently live on sewage and putrefying substances decreased the possibility of infection with typhoid or paratyphoid fevers.

Continued

3. The Hebrews also showed great concern for sexual hygiene. Basic to this was their practice of circumcision. This is a practice for which modern medicine has found a sound rationale, although the concerns of the Hebrews were originally religious in character: circumcision being the sign of a male who shared fully in the life of the Hebrew community. Although endogamy was found in the pre-Mosaic period, it is expressly forbidden in Lev. 18:6–18. The act of coition is regulated by many prohibitions, such as the forbidding of intercourse during menstruation (Lev. 20:18) and after parturition until the baby has been weaned. These prohibitions are all linked with the Hebrew abhorrence of blood and all bodily discharges. Deviations of sexual practice such as homosexuality and bestiality were condemned. (Lev. 18:22–23). In all of this the Hebrews lived on a far higher plane than did their neighbors in the ancient world, particularly the Canaanites, among whom deviations, promiscuity and prostitution were religiously acceptable.

4. The Hebrews were unique in the ancient world for their interest in cleanliness and sanitation. They stressed greatly the importance of washing the body despite frequent shortages of water that affected people in the semi-arid land they inhabited. Great care was also shown in disposing of excreta. Armies in the field were commanded to dispose of all bodily wastes by burial. (Deut. 23:12–13). The importance of such a measure in controlling air-borne and fly-borne diseases is tremendous.

The unique contribution of the Hebrews to medical theory and practice was in the area of preventive medicine. The great Mosaic legislation as interpreted and applied in the Old Testament guided this ancient people well for generations. Moral holiness was the basis for a profound betterment of man's physical well-being. Their faith in God as Creator of man as both a physical and spiritual being lead them to see the question of health as basically a single concern — the concern for each man as a child of God possessed of a sound spirit in a sound body.

Donald G. Dawe, Th.D.
St. Paul, Minn.

Concurrent Postgraduate Education and Teaching Appointments

In recognition of a variety of educational needs the Departments of Medicine and of Pediatrics at the University of Minnesota are offering full time staff appointments of one to twelve months duration to qualified internists and pediatricians who may desire a working sabbatical leave from practice. This program is supported by a grant from the Louis W. and Maud Hill Family Foundation.

This is primarily a teaching appointment; however, a major portion of time is free for participation in the clinical or laboratory area the physician may choose.

Applications and requests for further information should be addressed to either James B. Carey, M.D., Department of Medicine or Edward C. Defoe, M.D., Department of Pediatrics, University of Minnesota, Minneapolis 14, Minnesota.

He thought as a sage, but he felt as a man. — James Beattie

Curbstone Consultation

Spontaneous Pneumothorax

QUESTION: An 18-year-old male was treated by bed rest with his third verified spontaneous pneumothorax of the right lung in the past 24 months. The present chest X ray is described as "normal." What should I recommend as to future activity for this man? *M.D., Minneapolis*

ANSWER: The consultant assumes that in the episodes of pneumothorax the air is completely reabsorbed from the pleural space as proven by follow-up chest roentgenograms. After three such episodes, the likelihood of further pneumothoraces is quite high, 60-80%. The underlying cause is usually bleb formation—probably congenital "bronchopleural cysts" in reality—which continues to rupture. A life-threatening tension pneumothorax can occur. In approximately 10-15% of the patients, bilateral spontaneous pneumothoraces can prove hazardous.

In the past, attempts to fuse the visceral and parietal pleura by instillation of irritants during thoracentesis have not been successful. Open thoracotomy, resection of the blebs, and mechanical and chemical irritation of the entire parietal and mediastinal pleura is the most conservative and effective therapy and the treatment of choice. Removal of the parietal pleura should NOT be done and is totally unnecessary.

Neck Murmur

QUESTION: Is there any straightforward way that one can discern whether a murmur in the neck signifies cardiovascular disease or simply represents a venous hum? *M.D., Mankato*

ANSWER: A cervical venous hum can be heard in approximately a quarter of all adults. Though it can be heard almost anywhere over the lower anterior neck, it is most frequently detected and loudest at the lower lateral borders of the sternocleidomastoid muscles. The Valsalva maneuver will almost universally obliterate the murmur. The most reliable and simplest way, however, to identify a cervical venous hum is to occlude the internal jugular vein by light finger pressure just lateral to the thyroid cartilage while simultaneously listening to the murmur with the stethoscope. When the murmur is due to a venous hum this maneuver will result in immediate and complete disappearance of the bruit.

Man was made at the end of the week's work when God was tired.—Mark Twain

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Fracture — Trauma Conference

Colles' Fracture

(Continued from January issue of Minnesota Medicine)

Treatment of Unstable Colles' Fractures

Intramedullary Fixation (Author's Method)

Certain of the Colles' fractures are unstable at the initial reduction; post-manipulation films show that they do not hold either before or after the application of the cast. In such instances, transfixion Kirschner wires can be inserted through the distal fragment into the proximal fragment. Reduction is accomplished in the usual way with traction, flexion and pronation. The assistant holds the hand and wrist in flexion and pronation and steadies the forearm. Two .062″ diameter Kirschner wires are used. The longitudinal placement of one wire through the distal fragment and along the dorsal cortex of the radius upward about three inches into the forearm is preferred. A second wire is placed from the radial styloid of the distal fragment at about a 45° angle across the forearm into the ulnar side of the radius on the proximal side of the fracture. Anteroposterior and lateral X rays will show the reduction and placement of pins. Wires are cut below the skin surface. A short arm cast is applied with the wrist in slight flexion. Reduction has not been lost in such cases by simply using the forearm cast rather than the above elbow cast. Cast and wires are removed in six weeks. It is indicated in those fractures which have slipped in the plaster cast during the first or second week and require a second reduction.

Kirschner Wire Traction — Fig. 4

In those comminuted distal radius fractures with no stability on reduction so that shortening is inevitable, a method of remote Kirschner wire traction fixation is utilized. One wire is placed transversely through the second and third metacarpals toward the base to avoid the interosseous muscles and a second wire is inserted near the elbow through the ulna. The reduction is accomplished after the pins have been inserted. A plaster cast is used, incorporating the wires and the forearm. Occasionally the elbow is included. The cast and wires are maintained for eight weeks.

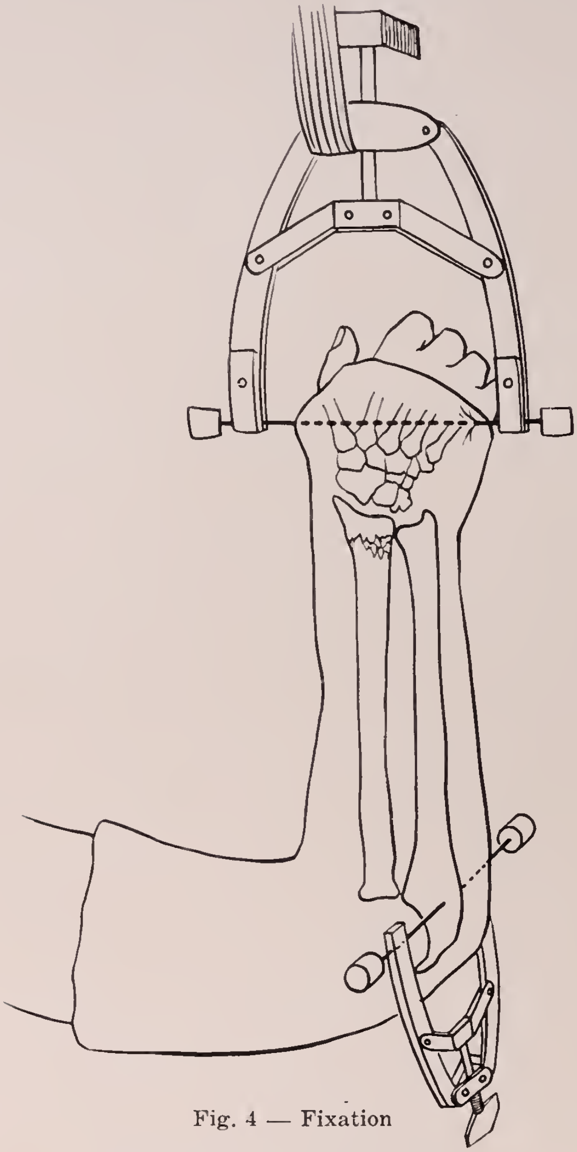

Fig. 4 — Fixation

Complication of Colles' Fracture

Early complications include median neuritis and initial swelling and fibrosis; late complications are those of stiffness of the fingers and the shoulder.

Severe Swelling

In those instances where severe swelling occurs or where median nerve palsy eventuates, the cast is split on the ulnar side and spread one-half inch or so. It is better to lose reduction and remanipulate than to cause a compression neuritis of the median nerve. Excessive swelling results in fibrosis, thereby delaying the regaining of motion of the fingers and the wrist.

Compression Neuritis

A few cases have been encountered in which the volar carpal ligament has been surgically divided for relief of compression neuritis of the median nerve. Compression neuritis occurred in one instance where the wrist was placed in 20° of flexion. The individual tolerance for flexion on the injured wrist is variable.

Atrophy

Atrophy of the hand, chronic swelling, stiffness of the fingers, wrist, elbow and shoulder may supervene from Colles' fracture. Extreme bone atrophy or osteoporosis also occurs. This is a radiologic reflection of the extreme bone change; but all other tissues likewise are atrophic and debilitated, a condition referred to as reflex sympathetic dystrophy or Sudek's atrophy. Treatment consists of exercise of fingers and all joints to tolerance. Analgesics are helpful; systemic Cortisone may be beneficial. When available, supervised physical therapy is advantageous. Recovery is prolonged over months, but may be surprisingly great.

Prevention of this disabling condition is early soft tissue care, elevation, avoidance or early correction of neuritis, and local and general body exercise.

Arthritis

Occasionally a hand will appear affected with acute rheumatoid arthritis, following the Colles' fracture. Such a condition may be actually a rheumatoid arthritis but is more likely a dystrophy; however, it may beneficially be treated as rheumatoid arthritis.

Rupture of Extensor Tendon

A late complication of undisplaced fracture is rupture of the long extensor tendon of the thumb. It is rare in fractures requiring manipulative reduction. Repair is by transfer of the extensor indicis proprius to the extensor pollicis longus distal to the wrist.

Other Fractures of the Distal Radius

Barton's Fracture

The partial articular fracture of the volar portion of the distal radius permits dislocation of the carpus. This is frequently called a Barton's fracture. Immobilization in flexion and supination should be tried. It is frequently necessary to perform open reduction of the volar fragment with screw fixation to hold reduction. The dorsal partial fracture may be held in position with the wrist in the slight dorsiflexion. At this time the carpus is stabilized against the volar intact portion of the radius. Flexion of the wrist would permit the carpus to exert pressure on the dorsal lip, thereby promoting recurrent dislocation and displacement of the dorsal fragment. Perhaps direct transfixion Kirchner wires are indicated in such cases.

Smith's Fracture

The reversed Colles' fracture (Smith's fracture), with volar angulation and anterior displacement of an intact distal articulation, is reduced in opposite manner from the Colles' fracture. Shortening may ensue due to comminution. Traction, dorsiflexion and supination are indicated for reduction. Immobilization is in dorsiflexion, supination of the wrist and right angles of the elbow.

Summary

The Colles' fracture is the most common fracture of a major bone. It may be easily reduced but is difficult to hold. The surgeon should critically analyze the postmanipulation X rays and those taken one or two weeks following the manipulation.

If the radius shortens more than one eighth of an inch, or the articular surface of the distal radius falls dorsally, one must consider another manipulation. No problems have been encountered in secondary reduction one or two weeks after the original injury.

Internal fixation with Kirschner wires is advantageous in the unstable Colles' fracture.

Kenath Sponsel, M.D.
Minneapolis, Minn.

Continued

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Galen's Cure for Upper Respiratory Infection

In this case "Galen administered the following heroic treatment to a woman at Rome who was afflicted with catarrh to the point of throwing up blood. He did not deem it wise to bleed her, since for four days past she had gone almost without food. Instead he ordered a sharp clyster, rubbed and bound her hands and feet with a hot drug, shaved her head and put on it a medicament made of doves' dung. After three hours she was bathed, care being taken that nothing oily touched her head, which was then covered up. At first he fed her only gruel, afterwards some bitter autumn fruit, and as she was about to go to sleep he administered a medicament made from vipers four months before. On the second day came more rubbing and binding except the head, and at evening a somewhat smaller dose of the viper remedy. Again she slept well and in the morning he gave her a large dose of cooked honey. Again her body was well rubbed and she was given barley water and a little bread to eat. On the fourth day an older and therefore stronger variety of viper-remedy was administered and her head was covered with the same medicament as before. Its properties, Galen explains, are vehemently drying and heating. Again she was given a bath and a little food. On the fifth day Galen ventured to purge her lungs, but he returned at intervals to the imposition upon her head. Meanwhile he continued the process of rubbing, bathing, and dieting, until finally the patient was well again, — a truly remarkable cure!"*

A "cure" truly remarkable in that the patient survived the treatment!

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*Thorndike, Lynn: See Minn Med Oct. '63.

When in Doubt

When you are in doubt whether an action is good or bad, abstain from it.— Zoroaster

Tumor Conference

Palliation in Metastatic Carcinoma of the Breast

EACH YEAR 54,000 females develop cancer of the breast. Twelve per cent of the cases are not resectable by generally accepted criteria of operability, and one half will die of the disease within five years. It is estimated that there are 141,000 women with cancer of the breast living in this country, some with undiagnosed lesions and some with residual lesions.[1] The problem of treating these patients with advanced, recurrent, metastatic breast carcinoma is a problem that must be faced often by every physician in general practice. Each patient is unique; each tumor reacts differently in different hosts; treatment is unpredictable, specific prognosis in the individual case impossible. It is important to establish the potential responsiveness of the tumor in each patient, and individualize the treatment.[2]

Case Report

A 43-year-old white married female was admitted to The Swedish Hospital March 18, 1962, complaining of a painful lump in the right breast, a hard nodule in the right supraclavicular region, a sensation of bloating of the abdomen, polydipsia, polyuria, and blurring of vision of the right eye and diplopia.

She said that she had had the "flu" in January, 1962, and after this noticed the polydipsia and polyuria. She had lost thirty pounds since the first of the year, but had been dieting. She noticed the lump in the breast two weeks prior to admission, and after palpating the breast lesion found the supraclavicular mass. Dimpling of the skin over the breast lesion was noticed just prior to admission, and it was this finding that caused her to consult her physician. The diplopia and blurring of vision had been present for one month.

She remembered that in April of 1961 she had carefully examined her breasts, and there was no palpable evidence of breast disease at that time. There was no family history of carcinoma of the breast. The patient had always enjoyed good health; she had been bothered with asthma, eczema and hay fever, and stated that antihistamines made her nervous, and that she was allergic to sulfonamides and penicillin. She was menstrating regularly and normally. She has three children.

Physical Findings

On physical examination an indurated mass was found under the right superior border of the orbital ridge producing some protrusion of the right eye. Diplopia was present. A hard, fixed lesion measuring 2 x 4 x 1½ cm. was palpated in the right supraclavicular region. In the right breast a hard, firm, fixed nodular mass measuring

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5 x 5 x 7 cm. was palpated. The skin overlying the mass was dimpled, and the nipple was retracted. A node measuring 2 cm. in diameter was present in the right axilla. Diffuse, freely moveable, nontender nodular masses were palpable in the abdomen.

Laboratory Findings

Laboratory examination gave the following results: hemoglobin 12.6 gm. per 100 cc. of blood, leukocytes 4,700 per cubic millimeter of blood with 65% neutrophils, 27% lymphocytes, 5% monocytes, 2% eosinophils, and 1% basophils. Serum calcium was 9.2 mg., phosphorus 3.8 mg., fasting blood glucose 102 mg. per 100 cc. of blood, alkaline phosphatase 22.5 King-Armstrong units. The urine had a specific gravity of 1.002; quantitative urinary calcium was 12.7 mg. per 2-hour sample.

Roentgenographic examination gave evidence of widespread bony abnormalities believed to be mixed osteoblastic and osteoclastic metastasis. On the skull films, ill-defined radio-lucensies were seen in the frontoparietal region.

Diagnosis

A diagnosis of carcinoma of the breast involving the skin and pectoral muscles, with metastasis to the axilla, the supraclavicular nodes, the abdomen, the supraorbital region and the lumbosacral spine was made.

Treatment

Ovariotomy

The problem was fully explained to the patient, and laparotomy for ovarian extirpation and biopsy of the abdominal masses was done on March 21, 1962. The abdominal cavity was studded with hard, metastic nodules involving the mesentery, the omentum, the Fallopian tubes, and the peritoneum of the cul-de-sac. There was no evidence of bowel obstruction. The right ovary was cystic, and on pathological examination found to contain a papillary mucin producing cystadenoma; the left ovary contained follicular cysts. The peritoneal implants were found to be small-celled metastatic carcinoma.

Pitressin

The patient did very well postoperatively. On her third postoperative day a pitressin test was done, confirming the diagnosis of diabetes insipidus. She was started on Pitressin .25 cc. every six hours. Prior to treatment with Pitressin, her daily urinary output ranged from 5,450 cc. to 8,685 cc.; after the Pitressin was administered she excreted 2,000 cc. to 3,000 cc. daily.

Cobalt Radiation

On her sixth postoperative day, the patient was started on cobalt radiation therapy. It was elected to irradiate only the symptomatic supraorbital lesion and the lumbosacral spine. By this time, a decrease of the supraorbital lesion was noted. Radiation therapy was followed by some nausea and vomiting, but on the fourteenth day after surgery she was discharged from the hospital, and continued her treatment on an outpatient basis.

Continuing Care

She was advised to take 100 mg. of cortisone daily, Pitressin as needed to control symptoms, and to wear a Jewett extension brace to protect the lumbosacral spine from fracture.

Continued

Progress

The patient has continued to do well and was last seen on her monthly visit October 9, 1963. She wears her brace, but has no pain when she does not wear it. She takes the Pitressin every 32 to 48 hours to control the diabetes insipidus. Her vision is normal. Her only complaint is her good appetite and her problem of gaining weight.

The supraclavicular, axillary nodes, and the nodule in the right upper quadrant of the abdomen have remained the same size as noted on her discharge from the hospital. The breast lesion has not enlarged. There is no dimpling of the skin. These lesions are carefully watched, palpated, and measured to signal the time for institution of additional palliative measures. She has no abdominal symptoms. The abdominal mass remains the same size.

Comments

Surgery, radiation, hormones, steroid administration, and chemotherapy are the measures available for palliation of metastatic carcinoma of the breast. The problem of which should be used and where and when is difficult. It seems logical to treat the symptomatic lesions initially with the most effective treatment, namely radiation, simultaneous use of a modality giving a total body effect such as ovariectomy, hormone administration or chemotherapy as indicated. In this case, the supraclavicular and axillary nodes, not influenced by the effect of radiation, demonstrate the effect of estrogen withdrawal and adrenal suppression by cortico-steroid administration. Should these nodules enlarge, further radiation or adrenalectomy may be indicated. In this case, it may be that a metastatic lesion produced an hypophyseal destruction, and the patient is experiencing some benefit from pituitary destruction as well as the nuisance of diabetes insipidus. Should she develop intestinal obstruction from the peritoneal and mesenteric metastasis, surgical resection or intestinal bypass may be necessary. Androgenic hormones may be tried, and chemotherapeutic agents may eventually be indicated.

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Minneapolis, Minnesota

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Beware the middle mind that purrs and never shows a tooth.—E. Wylie

Heaven's help is better than early rising.—Cervantes

Industrial Medicine

Relationship of Occupational Medicine

There can be no real distinction drawn between the work of physicians in occupational medicine and that of private practitioners. Every physician, whether in private practice or in occupational medicine, must at some time apply principles of occupational medicine in the treatment of his patients. In the future all physicians will be called upon more and more to practice rehabilitation or some other phase of occupational medicine.

The total adjustment of an individual to his health and environment should be of equal interest and importance to men in occupational medicine and those in private practice. These two branches of medicine must work as a team toward a common goal. Private physicians and those in occupational medicine have a common responsibility for bringing the benefits of medicine to the people of the community in which they dwell. Every medical history on a private patient should include the questions, "Where do you work?" and "What do you do?"

Preventive medicine is the largest single benefit received by the employee through occupational medical practice. The most important preventive measures are the various physical examinations in industry, which include: preplacement, periodic or annual, postillness and special examinations. By reporting to his private physician for correction of any defects detected, the employee improves his health and increases his longevity, bringing long-range benefits to his family and the company for which he works. The private physician benefits by referral of a patient to him soon enough in many instances to prevent irreparable damage.

The periodic or annual physical examination is to counsel the employee throughout his working career in matters that will help him to improve or maintain health, to safeguard the health and safety of others, and to discover and control the effects of possible unhealthful exposures in the working environment.

The physician practicing occupational medicine must benefit his employer and the community by keeping the maximum number of workers functioning at an optimum level of efficiency, and by guiding the employee in the correction of defects by using the services of private practitioners in his community. Close co-operation between physicians in occupational medicine and those in private practice can help maintain smooth patient relationships in difficult situations involving sick leave and other benefit plans in industry.

Plant physicians frequently examine workmen returning to the job after a serious illness, especially nonindustrial illness. The plant physician usually has the final responsibility for determining the patient's physicial limitations as they relate to his placement on the job, since he is in a better position to understand the job requirements, working conditions or occupational hazards in a given plant. He is also aware of the number of light-duty or modified-duty jobs available. The plant physician should have the co-operation of the private physician and supply necessary information on job requirements, working conditions, or occupational hazards. The private physician is then in a better position to discuss with his patient the need for further treatment and observation before the patient returns to work.

John A. Williams, M.D.
Committee on Occupational Health
Minnesota Medical Association

There are few pains so grievous as to have seen an exceptional man miss his way and deteriorate.—Nietzche

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Anticoagulant Therapy*

In 1941 Link and Campbell of the University of Wisconsin reported the isolation and crystallization of the agent responsible for hemorrhagic sweet clover disease in cattle. It was but a brief interval between the discovery of the drug and its use in the treatment of thromboembolic conditions in man.

The list of conditions for which a prolonged course of anticoagulant therapy is indicated is continually lengthening. Among these are recurrent pulmonary emboli, recurrent thrombophlebitis, myocardial infarction, rheumatic heart disease, with embolization, auricular fibrillation, cerebral transient ischemic attacks, and recurrent cerebral thromboses.

It has been estimated that over one million persons in the United States received anticoagulant therapy of some duration last year. Further, it is estimated one third to one half of these are logical candidates for long-term therapy; from this the magnitude of the problem can be readily appreciated.[2]

This overwhelming statistic would seem to indicate that the prudent medical student should learn the fundamental concepts of coagulation and the basic principles of anticoagulant therapy.

Fig. 1** — Normal Coagulation

Stage 1 — Formation of a Prothrombin Activator in tissue and plasma.
Stage 2 — Conversion of Prothrombin to Thrombin by an activator.
Stage 3 — Conversion of Fibrinogen to Fibrin in presence of Thrombin.

Continued

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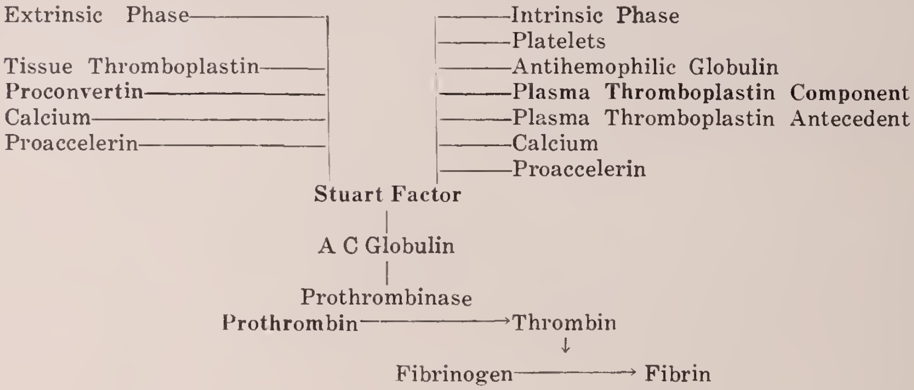
*Medical Grand Rounds, Mt. Sinai Hospital, May, 1962.

**Figure 1 from Green, R. A.: Hemorrhagic disorders. The Bulletin, St. Louis Park Medical Center, Feb., 1962.

†Figure 2 from Sise. S. H., Lavelle, M. S., Adamis, D. & Becker, R.: Relation of hemorrhage and thrombosis to prothrombin during treatment with coumarin-type anticoagulants. NEJM 259:266, 1958.

In anticoagulant therapy factors in Stages 1 and 2 are of primary interest. A simplified concept of the coagulation mechanism that is useful in discussing anticoagulants is as follows:

Fig. 2† — Current Simplified Concept of the Coagulation Mechanism


Extrinsic Phase
Tissue Thromboplastin
Proconvertin
Calcium
Proaccelerin
Intrinsic Phase
Platelets
Antihemophilic Globulin
Plasma Thromboplastin Component
Plasma Thromboplastin Antecedent
Calcium
Proaccelerin
Stuart Factor
A C Globulin
Prothrombinase
Prothrombin
Thrombin
Fibrinogen
Fibrin

The conversion of prothrombin can proceed by either of the two routes. The extrinsic phase, or tissue phase, is initiated by tissue injury causing a release of tissue thromboplastin. This then interacts with proconvertin, Stuart factor and calcium to form prothrombinase, a prothrombin activator. The last two stages are then initiated in turn and coagulation occurs.

The intrinsic phase, or plasma phase, entails the release of platelet thromboplastic factors from agglutinated platelets. This reacts with antihemophilic globulin, plasma thromboplastin, plasma thromboplastin antecedent, and calcium to generate plasma thromboplastin, which then reacts like tissue thromboplastin, and coagulation results.

The factors depressed by coumarin and indanedione derivatives are indicated in bold type on the diagram of the simplified concept of coagulation. The depression is secondary to the influence of these drugs on Vitamin K synthesis by the liver. The four Vitamin K dependent factors are prothrombin, proconvertin, Stuart factor, and plasma thromboplastin component. It is of importance to make special note that proconvertin functions only in the extrinsic, and plasma thromboplastin only in the intrinsic phase.

With this brief discussion we are able to proceed to the specific anticoagulants and the tests used to establish anticoagulant control.

Anticoagulants

Heparin and heparin-like substances cannot be used for long-term therapy because of expense and the necessity of daily injection. To be discussed at this time are the coumarin and the indonedione derivatives. Coumarin drugs include Dicumarol, Tromexan,® Morcaumor,® Cumopyrin, Warfarin and Sintrom.® The indanedione drugs include phenylindanedione, Hedulin,® and Dipaxin.®

Rodman, Ryan, and Pastor recently made a comparative study of four commonly used anticoagulant drugs: bishydrovycoumarin (Dicumarol), Warfarin (prothromadin), phenindione (Hedulin®) and diphenadione (Dipaxin®).

The study was on eighty relatively healthy subjects in whom there was no therapeutic indication for anticoagulant therapy. The objectives of the study were: first, to gain information regarding onset of action, peak, effect, duration of effect, and variability of effect of the four drugs; second, to compare the conventional induction schedule of bishydroxycaumarin with a more radical dosage program; and third, to compare the optimum induction dosage programs of the four drugs.

Prothrombin Activity

Twenty subjects with prothrombin activity over 80 per cent were divided into four groups and given a single large dose of one of the four anticoagulants. The dosages used were bishydroxycaumarin 600 mg., dephenadione 60 mg., phenindione 600 mg., and Warfarin 90 mg. These dosages were chosen on the premise that they were of approximately equal prothrombinopenic effect. The prothrombin activity was tested by the method of Quick for control purposes.

They found the onset of action of all four drugs to be between the eighth and sixteenth hours. The peak effect for phenindione was obtained in thirty-two hours and for the other three drugs in forty hours. The duration of effect of any drug was variable from patient to patient as well as from drug to drug.

The aspect of the study comparing the conventional dosage schedule of bishydroxycoumarin to a more radical schedule revealed the following:

TABLE 2*
Comparison of Induction Dosage Schedules of Bishydroxycoumarin

	Percentage of Patients in Therapeutic Range At —	
Dose	Forty Hours	Sixty-four Hours
300 mg. first day) 200 mg. second day)	0	67
600 mg. first day) 100 mg. second day)	50	100

In the third phase they divided forty-eight subjects into four groups. The induction program was based on clinical judgment and varied slightly according to the initial prothrombin activity. In each case, however, one large initial dose was given, followed by a maintenance dose.

The following table contains the recommended dosages.

TABLE I**
Recommended Initial Dose

	Dose with Control Prothrombin Activity of:		
Drug	80-100 Percent	60-80 Percent	50-60 Percent
Bishydroxycoumarin	650 mg.	600 mg.	550 mg.
Diphenadione	60 mg.	55 mg.	50 mg.
Phenindione	500 mg.	450 mg.	400 mg.
Warfarin	75 mg.	70 mg.	60 mg.

Continued

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*Table 2 From Rodman, et al.: A comparative study of four prothrombinopenic anticoagulant drug properties. Amer J Med 27:411, 1959.

**Table 1 from Rodman, et al.: Ibid.

Of the twelve subjects who received the recommended dose of Warfarin, ten were in the therapeutic range forty hours after the initial dose. Nine patients given phenindione, eight given diphenadione and six given bishydioxycoumarin were in the therapeutic range at forty hours. Two of the twelve subjects who received Warfarin had a prothrombin activity less than 10 per cent at sixty-four hours.

The variations in dosage response may be related to the prothrombinopenic effect and the rate of catabolism of the agent. Although prothrombin time depression was fairly uniform in a single large dose, there were wide variations in the duration of effect. This suggests that the rate of metabolic breakdown and excretion are important determinants of dosage.

Clinical Evaluation of Different Anticoagulants

The authors of the above report then went on to a clinical study to compare the four prothrombinopenic anticoagulant drugs.[8] The drugs were given to 287 patients for an average of twenty-five days per patient. Large initial induction doses were used when there was no contraindication present. A control experiment with bishydroxycoumarin was carried out comparing the effect of a conventional dose to the larger recommended dose.

The large initial dose was given 134 patients and of this group only five had transient depression of prothrombin activity below 10 per cent. None of the five had evidence of hemorrhage at the time of this depression. The onset of action of all four drugs was at approximately twelve hours and by sixteen hours there was almost always depression of prothrombin activity. The degree of early depression did not appear to correlate with the magnitude of the peak effect which occurred at about forty hours. The sixteen-hour check has as its primary value the picking up of an occasional hypersensitive individual whose prothrombin activity has dropped to or below the therapeutic level. If the sixteen-hour value merely reflected a minimal depression, a maintenance dose was given. The forty-hour check is then the guide in determining the subsequent dose.

The data suggested that patients who received bishydroxycoumarin or diphenadion were more readily maintained within the therapeutic range than those who received Warfarin or phenindione. The average maintenance doses were 90.7 mg. bishydroxycoumarin, 6.9 mg. diphenadion, 97.6 mg. phenindione, and 7.7 mg. Warfarin.

There was relatively wide variation in dosage requirements in the same patient from day to day and among patients receiving the same drug. This was less with bishydroxycoumarin and diphenadione, but the differences were not sufficient to be clinically useful.

In the experiment comparing the usual initial dose of bishydroxycoumarin — 300 mg. the first day followed by 200 mg. the next day, to a large initial dose 500 to 650 mg. the first day followed by 100 to 200 mg. the second day — it was found that only 29 per cent of the patients in the first group were in the therapeutic range compared to 71 per cent of the second group at forty hours. The authors felt the large initial dose procedure facilitates the early establishment of a therapeutic level and eliminates the wide fluctuations frequently seen in the first few days when a conventional dose is used.

In summary, the authors felt none of the four drugs had enough advantages to warrant recommending it over the others. The one advantage peculiar to Warfarin is that it can be used parenterally.

Laboratory Control of Anticoagulant Therapy

The basic principle behind the tests of the clotting system is the addition of a reagent containing all the factors in optimal quantity except the factor or factors being measured. The following diagram** makes it immediately apparent which factors are being tested by the four tests of value in anticoagulant control at present.

	Quick Prothrombin Time	Thrombotest	Prothrombin-Proconvertin	Prothrombin Assay
Thromboplastin	Saline Brain Extract	Saline Brain ext. + Phospholipid + Baso$_4$ Ads. Plasma	Saline Brain Extract	Saline Brain Extract
AHG				
*PTC				
Fibrinogen		Baso$_4$ Absorbed Plasma	Baso$_4$ Absorbed Plasma	Baso$_4$ Absorbed Plasma
Proaccelerin				
*Stuart Factor				Serum Eluted BaSO$_4$ Adsorbate
*Proconvertin				
*Prothrombin				

*Decreased with anticoagulant therapy (Vit. K Dependent.)

The Quick One-Stage Test

The Quick one-stage procedure, or a modification of the procedure, has been the most widely used test for laboratory control of anticoagulant therapy with prothrombinopenic drugs.

The Quick test is a measure of the time needed for the thrombin titer of plasma to reach the clotting level in the presence of a fixed amount of calcium and thromboplastin. The clotting time is thus influenced by all the factors which are decreased by anticoagulant therapy except plasma thromboplastin. There will also be a low prothrombin time if fibrinogen and proaccelerin are depressed.

Criticisms of this method include its insensitivity to prothrombin and proconvertin in concentration above 50 per cent of normal, making it impossible to follow the initial decrease in coagulability. The specified calcium concentration used is not optimal when the blood being tested has an abnormal hematocrit, and the test is sensitive to small amounts of heparin. A greater defect, however, is the fact that "prothrombin time" is changed by aging of the plasma. Initially there is partial activation of proconvertin producing a falsely short "prothrombin time," and this is followed by an inactivation of proaccelerin causing a falsely long "pro-

Continued

**Abridged from Gonyea, L. M. and Bridges, R. A.: Laboratory control of anticoagulant treatment with coumarin derivatives. University of Minnesota Medical Bulletin No. 4 :164, Jan. 1962.

thrombin time." This factor makes it necessary that samples be tested shortly after being obtained.

The Thrombotest

In 1959 Owren described a new method of control of anticoagulation which he called the "thrombotest." The advantage of this test was stated to be its sensitivity to all four of the factors depressed by anticoagulants, and it is possible that this test will replace the Quick test.

Comparison of Tests

In 1961, Moore and Beeler of the Ochsner Foundation Hospital performed a comparison study of the Quick test to the thrombotest. The results were evaluated by plotting the prothrombin time index against the thrombotest index. The index was calculated by dividing the patient's time in seconds by the control time in seconds. Seventy-seven of the specimens were found to be in the therapeutic range by prothrombin time. Nineteen of this group were also in the therapeutic range by the thrombotest, but the remaining 58 were below the lower limit of the thrombotest therapeutic range. An additional 11 specimens from seven different patients were below the therapeutic range by prothrombin time but were in the therapeutic range with the thrombotest.

The reproducibility of the thrombotest was good; the standard deviation for tests in the normal range was .66 seconds and for those in the therapeutic range, 1.44 seconds.

The authors concluded that the thrombotest is a practical, reliable method of control of anticoagulant therapy. However, the accepted therapeutic range by the prothrombin time and the therapeutic range suggested by Owren for control by the thrombotest appear to result in different levels of anticoagulation. They did make the point that the difference in the two levels could reflect the difference in thromboplastin used in their laboratory.

Results of Therapy

Long term anticoagulant therapy is being implemented in a growing list of diseases. Its largest and perhaps most controversial use is in the treatment of myocardial infarction and angina pectoris on a long term basis.

Manchester has carried out a study at the Washington University School of Medicine in which he followed a group of patients for one to ten years, 204 on anticoagulant therapy and an alternate 200 control patients.

Subsequent Infarction

The incidence of subsequent infarction was three times greater in the control group; the mortality rate expressed on a per hundred patient years' basis was eight times greater in the control group. In addition the incidence of thromboembolic complications was only 5.8 per cent in the anticoagulated group compared with 17.5 per cent in the control group. The respective mortality in those suffering this complication was 14.2 per cent and 45.7 per cent. The overall mortality due to thromboembolic phenomena and hemorrhage was 7.8 per cent in the anticoagulant group and 42.5 per cent in the control group.

Mortality

In this study the prothrombin time was maintained at 25 to 35 seconds by the authors' capillary blood prothrombin test. This is roughly equivalent to 30 to 40 per cent Quick prothrombin activity.

Owren reported a mortality rate of 4.2 per cent in the first group and 4 per cent in the latter group after a total of 609 treatment years, less than half the mortality rate shown by statistics of a similar group not treated with anticoagulants.

Recurrence-Free Incidence

Thomas, Scallen and Savage of Minneapolis published a retrospective study in 1961 that was designed to answer the question of the value of long-term therapy.[15] By the survivorship table method they estimated that 803 per 1000 patients remained recurrence-free for 60 months when therapy was continued compared to 365 per 1000 patients remaining recurrence-free for 60 months after discontinuance of therapy.

When using this method in comparing mortality it was estimated that at the end of 60 months of continuous therapy 736 per 1000 patients would be surviving compared to 672 surviving at 60 months after discontinuance of therapy. The small difference between these two groups is readily obvious, but the results are biased by the fact that therapy was resumed for short intervals in nonfatal recurrences in the latter group.

This is an interesting aspect of any discussion on anticoagulant therapy, but further discourse will not resolve the argument at this time. There are studies being conducted at present to resolve this controversial problem.

Complications and Contraindications

It was but a short time after anticoagulants were introduced that complications of therapy occurred. In retrospect this could easily have been predicted. Doctors unfamiliar with the drug and its actions were administering it without adequate control tests.

Organ Disease

Contraindications to anticoagulant therapy as listed by Duff are significant hepatic or renal insufficiency, ulcerative lesions of the gastrointestinal tract, blood dyscrasias with a bleeding tendency, subacute bacterial endocarditis, recent surgery on the brain or spinal cord, recent threatened abortion, and near-term obstetric case. The most significant contraindication is lack of a good laboratory to run control tests.

Gastrointestinal Bleeding

In 1960 Gurewich listed as the most frequent hazards gastrointestinal bleeding, hematuria, subcutaneous ecchymosis, epistaxis and hemoptysis. Rarer hazards include spontaneous spinal epidural hematoma, bilateral adrenal hemorrhage, retroperitineal hemorrhage, hemopericardium, intraperitoneal hemorrhage of ovarian follicular origin, and hemorrhage into the breast.

Continued

Intramural Hemorrhage

Intramural hematoma of the intestine may occur as a result of trauma as well as secondary to a blood dyscrasia. The roentgenologic findings in these cases were first described by Liverud in 1948. He commented on the filling defect of the lumen and the prominent folds of mucosa demonstrated after administration of barium. There is a "coil spring" appearance created by folds of mucosa made prominent by edema and hemorrhage.

Treatment of the Complications

The choice of treatment in these cases is controversial. Pearson feels conservative management is contraindicated and advocates laporotomy, resection, and entroenterostomy. In contradistinction Beamish reported seven cases, all of which had been successfully managed conservatively. In a poor risk surgical candidate in whom the diagnosis is made with fair certainty the wisest course would probably be conservative therapy.

The frequency of hemorrhagic complications in the larger studies has been low. An example is the study of Rodman et al. They maintained 287 patients on anticoagulants for a total of 7,165 patient days. During this period six major and seventeen minor bleeding episodes occurred, a rate of 8 per cent or approximately one complication for every 315 days of therapy. The most frequent major complication was gastrointestinal hemorrhage. Of the five patients two expired a few days later, but the deaths were not attributed directly to the bleeding episodes. The other major complication was massive hemoptysis in a patient with advanced rheumatic heart disease and recurrent pulmonary infarction. The most frequent minor complication was hematuria. It is of interest that all but four of the hemorrhagic episodes occurred when the prothrombin activity was in the therapeutic range.

Manchester had 53 (3.5%) bleeding episodes in 1,500 patients who received anticoagulants over a twelve-year interval. Owren has quoted the range of frequency of complications as being between 5-15 per cent. The number of complications reported in the studies probably does not reflect the percentage occurring in private practice. This can be attributed to the more "ideal conditions" created in a study for control of therapy.

Complications other than hemorrhage are rare. Rodman et al. have reported one case in which the patient developed fever, scarlatiniform eruption and eosinophilia, and two cases of agronulocytosis, fever, and scarlatiniform eruption. Tragge et al. reported a case of idiosyncracy to Dicumarol in which the prothrombin activity responded poorly to intravenous mephyton.

Case Report

A 74-year-old white retired male, was hospitalized at another hospital in April, 1961, because of severe angina pectoris. An electrocardiogram at that time revealed interventricular block and left ventricular ischemia. It was also noted that he had diabetes mellitus of approximately 10 years duration, well controlled with oral hypoglycemics and diet; he also had hypertension of about the same duration. Because of the severe angina he was started on Dicumarol. Other medications were 0.1 mgm. digitoxin daily, Diabinese, and nitroglycerine as needed.

On March 30, 1962, he came to the Outpatient Department on a routine follow-up visit. However, at this time he complained of severe back pain that had become more bothersome over the preceding two months. He had also become constipated and showed slight weight loss. Because of these difficulties it was felt that neoplasm of the colon should be ruled out. Proctoscopic examination was negative to 25 cm. He was scheduled for a barium enema examination on April 2, 1962. While he was in the clinic a prothrombin time was done and found to be 38.9 seconds with a control of 13.5 seconds. He was told not to take any Dicumarol for the next two days and then to again resume the 25 — 12.5 schedule on which he had been maintained.

The following day, April 3, 1962, he had onset of vague abdominal discomfort, anorexia, and constipation. These symptoms continued into the next day and that evening he elected to give himself a tap water enema. He had return of "black stool" but his symptoms continued. Later that evening he developed severe hypogastric pain and was unable to sleep. At 2 A.M. on April 5, 1962, he had an emesis of what was described as black material. He again vomited at 8 A.M. Because of continuing difficulty he came to the outpatient department and was admitted to Mt. Sinai Hospital at 3:30 P.M.

On initial examination the patient appeared anxious and complained of severe bilateral lower abdominal pain. Vital signs were: blood pressure 135/65, pulse 80, and rectal temperature 99°. Mucous membranes were dry, skin turgor poor. Lungs were clear; there was a Grade I systolic murmur along the lateral sternal border. The abdomen was minimally distended; tympanitic, and bowel sounds were hypoactive. He had guarding and tenderness to direct palpation; rebound tenderness was questionably present. Obturator and psoas signs were negative, as was rectal examination.

An electrocardiogram was obtained and read as not being significantly changed. A flat and upright of the abdomen showed no free air and no dilated bowel. An initial CBC showed Hgb 14.3, WBC's 15,000 with 90% PMN's.

At 9:30 P.M. he had a 30-50 cc. emesis of dark material which was tested and found 2+ guiac. At 3 A.M. he was catheterized and 250 cc. of urine obtained. Urinalysis revealed specific gravity — 1.020, albumin — 1+, sugar — 1+, RBC's — 15 to 25/17 high power field, and WBC's — 21.4/high power field.

A repeat CBC in the morning, April 6, 1962, showed Hgb — 12.2, WBC's — 17,000, with 91% PMN's. Repeat flat and upright X ray of the abdomen, vital signs, and examination were not significantly changed from the previous evening.

At 10:45 A.M. we were informed that the prothrombin time was 21.0 seconds with a control of 12.2 seconds. A repeat test verified this result. He was immediately given 50 mgm. of Mephyton intravenously.

A surgical consultation was obtained and examination revealed definite dullness to percussion in the left lower quadrant and a fullness in this area. He also had definite rebound tenderness in the left lower quadrant and tenderness to direct palpation and guarding over the entire abdomen. An exploratory laporotomy was advised as soon as the prothrombin activity was normal.

He was given another 50 mgm. of Mephyton IV, which was again repeated two hours later. Whole blood was also started. The prothrombin time was 18.5 seconds with a control of 13.8 seconds at 6 P.M. The patient was taken to surgery at 6:45 P.M.

On opening the abdomen there was a large amount of dark red nonodorous blood. Exploration revealed a red-bluish area of discoloration of the jejunum and its mesentery. The arterial pulse was palpable at the base of the mesentery. In addition there were other areas of faint discoloration throughout the bowel and mesentery. The involved area was resected and an end-to-end anastomosis done to restore continuity. The patient tolerated surgery poorly, being shocky most of the time.

In the immediate postoperative period he was noted to have Cheyne-Stokes respirations and was hypotensive. Three to four hours after surgery his pulse was 130 — 140 per minute and his skin was cold and blotchy. He went into shock and expired the morning of April 7, 1962. The final impression was that the patient developed pulmonary edema, and the question of hypervolemia was raised.

Pathologic examination of the specimen revealed marked hemorrhage into the wall of the bowel and into the mesentery. On microscopic examination the mucosa was described as being normal; there was hemorrhage into the submucosa, serosa, muscularis propria and mesentery.

Summary

The indications for anticoagulant therapy and their use are growing. To use them to best advantage with a minimum of complications requires an understanding of their pharmacological effect and knowledge of the

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laboratory tests and the limitations of these procedures in establishing a therapeutic level. It is also well to remember that the major contraindication to therapy is the lack of a good laboratory to run to control tests.

It is established that anticoagulants are of value in the treatment of the acute phase of myocardial infarction. Whether or not they are of benefit on a long-term basis is not certain. Studies to evaluate this aspect are going on at present and will hopefully resolve this controversy in the near future.

Regarding complications it is sufficient to say, "In a patient on anticoagulants always consider hemorrhage when evaluating a complaint."

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18-31 can be obtained from Grand Rounds Editor at Mt. Sinai Hospital.

Responsibilities gravitate to the person who can shoulder them, and power flows to the man who knows how.—Elbert Hubbard

Abstracts, Briefs and Commentaries

PULMONARY EMPHYSEMA IN A NONSMOKING POPULATION

The authors note that in California the death rate from pulmonary emphysema has increased from 1.5 (1950) to 9.5 (1960) per 100,000 population. The three major theories of etiology of this disease are (1) airtrapping, (2) autoimmune response, and (3) occlusion of the nutrient bronchial artery.

As nicotine has a vasoconstricting effect, the authors compared epidemiologically the possible relationship of smoking and urban air pollution to the development of pulmonary emphysema.

This is a preliminary report of a five-year study of the mortality among the male population of the essentially nonsmoking, nondrinking religious group, the Seventh Day Adventists (S. D. A.). Otherwise the group differs little in population distribution, employment, etc. as compared to the general male population.

By death certificate analysis, the authors found that pulmonary emphysema was the listed cause or contributing cause of death in 18 males of the S.D.A. Seventy-three (73) deaths would have been expected. Available history indicated that 10 of the 18 men had been heavy cigarette smokers.

After analyzing the other variables, the authors conclude "that smoking, particularly cigarettes, may indeed be an important differential factor related to the risk of mortality from pulmonary emphysema."

Although cigarette smoking will undoubtedly continue, this type of report indicates that long term studies and education regarding the hazards of smoking should start among the teen age groups. The question of legislation and the free enterprise of the cigarette industry must be decided by appropriate facts.

Individually, I feel that cigarette smoking has an adverse influence on the physiology of the bronchopulmonary and the cardiovascular systems. Certainly, the chronic bronchitis of cigarette smokers is a definite additive hazard to surgical procedures.

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P. W. Dysinger, F. R. Lemon, G. L. Crenshaw. R. T. Walden, M.D.'s: Dis Chest 43:17, 1963

Continued

FATAL BILIARY SURGERY

Drs. Glenn and McSherry have brought the Cornell University Department of Surgery studies on biliary surgery up to date with a current evaluation of over 2,000 patients since 1950. There have been three periods of study in the past 50 years. In the early era of biliary surgery a 10 to 15 percent mortality pertained and deaths were attributable to far advanced biliary and liver disease. From 1932 to 1950 there was a decrease in proportion of deaths attributable to hemorrhage, shock, and intra-abdominal infection. However, liver disease, such as biliary cirrhosis and intrahepatic infection continued to account for a large percentage in the mortality. In the latter period the over-all mortality had dropped to 1.7 percent with the principal cause of death now being due to cardiovascular disease.

In elective cholecystectomy the mortality rate dropped to 0.3 per cent, therefore the authors suggest that lowering the mortality rate for surgical treatment of calculus disease of the biliary tract will result from performance of elective cholecystectomy prior to the onset of late sequelae and complications of long standing calculus disease. Cholecystostomy is recommended in the very poor risk patient. The 12.5 percent mortality in cholecystectomy is not considered as an indictment of the procedure but a reflection of the poor operative risk of these patients. Cholecystectomy was performed for acute cholecystitis on 266 patients with six deaths, a mortality of 2.3 percent. It is significant that in three, or half of the deaths, the gallbladder had perforated prior to the operation. Infection continues to be a major problem in that subhepatic abscess continues to appear.

It seems obvious that removal of calculus gallbladder prior to complications directly related to it will remain the safest procedure. The current evaluation of this study, which indicates the importance of cardiovascular evaluation, particularly in the elderly patient, can well be re-emphasized. The recent coronary attack being overlooked or missed in the presence of calculus disease in the gallbladder has all too frequently accounted for a surprise postoperative death with the postmortem revelation of a recent infarct of the myocardium preceding the date of operation. Careful cardiac evaluation, including electrocardiography, should aid in selection of the appropriate time for operation. The authors recommend three to four months following a coronary occlusion as the recommended waiting period for elective biliary surgery.

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Glenn, Frank, Mc Sherry, Charles K.: "Etiologic Factors in Fatal Complications following Operation upon the Biliary Tract." Ann Surg 157:695 May 1963

SYNOVIAL SARCOMA

Twenty-five patients bearing synovial sarcomas treated by the authors between 1950 and 1960 reveal a 5-year "cure" rate of 29%. The best results were obtained with patients in the older age group and those with the most distally located synovial sarcomas. A recurrence rate of 70% following conservative excisions performed elsewhere emphasizes the futility of this procedure. Resection of regional lymph nodes should be performed; such metastases occurred to them in 19%.

Courtesy of References and Reviews
Journal of the American Medical Association

Ariel, I., and Pack, G.
New Engl J Med 268:1272 June 6 1963

FUNCTIONING ISLET CELL TUMORS OF THE PANCREAS

The authors present a twenty-five year follow-up of the six patients with the syndrome of hypoglycemia surgically treated and initially described by Whipple in 1935. The historical backgrounds and several review articles dealing with adenomas of the islet cells are summarized. Case summaries are presented in detail for each of the six patients.

Three of the patients subsequently developed gastrointestinal bleeding from peptic ulceration. One of them expired as a result of the hemorrhage. Hypoglycemia could not be implicated as the cause for the ulcer diathesis, since in each case this had been corrected by surgery. Actually, two of the patients developed diabetes later in life. The relationships of noninsulin-producing and insulin-producing pancreatic adenomas and the peptic ulcer diathesis have yet to be clarified.

Initially there was excellent relief of neuropsychiatric symptoms in all six patients. Long-term follow-up, however, disclosed that five of the patients developed marked mental disturbances. There is some speculation that this may have resulted from prior irreversible brain damage caused by the hypoglycemia.

The authors conclude that despite immediate good results of excision of functioning islet cell adenoma, one must be cognizant of the possible development of peptic ulcerations. They also suggest that a very guarded prognosis be considered relative to the neuropsychiatric manifestations of the disease.

The particularly commendable feature of this study is the duration of the careful follow-up. In the instance of Whipples' Syndrome such study suggests the possibility of two unexpected clinical sequelae. One can only wish the series was of greater magnitude to permit statistical evaluation of the observations.

Robert N. Hammerstrom, M.D.
Minneapolis, Minnesota

"Functioning Islet Cell Tumors of the Pancreas: Twenty-five Year Follow Up"—Markowitz, A. M., Slanetz, C. A., and Frantz, V. K. Ann Surg., 154:877, Dec. 1961

LONG TERM ANTITETANUS IMMUNITY

Thirty veterans were studied 17 to 19 years after their last active immunization or toxoid booster injection. The effective level of antitoxin in the serum of each individual studied was tested by using a mouse bioassay technique. Serial dilutions of the serum were made and each was mixed with three median lethal doses of tetanus toxin which was then injected into the mouse.

Tetanus toxin given alone in a three-median lethal dose killed all mice. When mixed with the serum of the veterans previously immunized 17 to 19 years ago, approximately half the subjects studied exhibited protective levels of antitoxin prior to a current booster dose of toxoid. After administering a standard booster dose of tetanus toxoid to the remaining group. all but two exhibited protection after seven days.

The author suggests that the upper time limit for active immunization at which booster doses of toxoid produce a safe level can be further extended.

Harold D. Kletschka, M.D.
Syracuse, N.Y.

Worman, R. K., Kiss, Z., Camp, F. A., McDonald, K. E., and Schenk, W. G.: Residual Antitetanus Protection 17 to 19 Years After Immunization. SG&O 116:576, May 1963.

Continued

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UREMIC POLYNEUROPATHY

Symptoms and signs of sensorimotor neuropathy developed in four young adult patients who had long-standing renal failure due to chronic glomerulonephritis, pyelonephritis, hereditary interstitial nephritis, and obstructive uropathy with congenital anomalies. Pain, numbness, and tingling of the toes and feet were initial symptoms of the neuropathy. On examination of the peripheral nerves, destruction of both the myelin and the axis fibers of peripheral nerves was found, but this was more prominent distally. The authors suggested that polyneuropathy is the consequence of a metabolic disorder, and that in some manner it is dependent on severe and chronic renal failure.

Peter J. Dyck, M.D.
Rochester, Minn.

Asbury, A. K., Victor, M., and Adams, R. D.: "Uremic Polyneuropathy." Arch Neurol 8:413 April 63

PHLEBOGRAPHIC PATTERNS OF ACUTE DEEP VENOUS THROMBOSIS OF THE LEG

Phlebograms confirmed deep vein thrombosis in 100 extremities of 90 patients. The phlebograms were analyzed and correlated with the clinical findings.

Deep vein thrombosis was suspected if the patients had (1) calf pain, swelling, tenderness (71 cases), (2) picture of pulmonary embolism plus local leg signs (7 cases), (3) picture of pulmonary embolism without local leg signs (9 cases), and (4) severe superficial phlebitis (3 cases). Thirty-four per cent of the patients were postsurgical and 43% were performing their usual occupations. Seventy-eight patients were studied within nine days of their symptoms. Physical findings were tenderness, swelling. positive Homan's sign, and positive sphygomomanometer cuff test.

Deep venous thrombosis was considered present if there were well defined defects in opacified veins in two radiographs. The radiologic diagnosis was confirmed in thirty-two extremities by surgical exploration or necropsy.

The three general patterns of thrombosis were (1) lower leg venous thrombosis, (2) femoral vein thrombosis, and (3) ileofemoral vein thrombosis.

In lower leg thrombosis (43 extremities) ankle edema was absent or minimal and local tenderness the most constant finding. Homan's sign was positive in 44%, the sphygomanometer cuff test in 75%.

In femoral vein thrombosis, there is a high incidence of distal venous thrombosis, leg edema was present more frequently and often went above the knee, and Homan's sign was positive in only 60%, the cuff test in 50%.

Ileofemoral thrombosis resulted in leg swelling in 100% of cases, Homan's sign was positive in 48% and the cuff test in 57%. The saphenous vein was the important collateral in 74% of the cases. Distal venous involvement was present in many but localized ileofemoral thrombosis was present in about 50%.

Diagnostic tests and surgical relief of venous thrombosis should not be delayed. There is little risk from the test. Note that 43% of patients were doing their ordinary occupations.

Jerome T. Grismer, M.D.
Minneapolis, Minn.

J. A. DeWeese, S. M. Rogaff: Surgery 53, 99, 1963

Continued

PROTEIN ABNORMALITIES IN ULCERATIVE COLITIS

An antinuclear factor, which has been found in lupus erythematosus patients and their families, has also been found in ulcerative colitis. The sera of 98 subjects from 34 families with ulcerative colitis were examined for the presence of antinuclear and rheumatoid factors, thyroid antibodies, and positive lupus erythematosus (LE) latex tests. These were compared with a contratest group of relatives of gastric cancer patients. The antinuclear factor was found in 23% of the ulcerative colitis families, but only in 3% of the contratest group. The incidence of rheumatoid factor, thyroid antibody, and LE latex was the same in both groups.

Courtesy of References and Reviews
Journal of the American Medical Association

Thayer, W. and Spiro, H.: Gastroenterology 44:444 April 1963

TRAUMATIC HEMOBILIA

Traumatic hemobilia is bleeding through the biliary tract secondary to traumatic liver cavities in which vascular and biliary radicles communicate. Typical symptoms include history of trauma, pain simulating biliary colic, and gastrointestinal hemorrhage. A case developing after adequate repair of a liver laceration is reported. The importance of accurate diagnosis and definitive surgical correction are stressed. The authors suggest (1) a direct attack on the bleeding source in the liver by (a) ligation of the bleeding artery in the liver cavity if possible, (b) ligation of the appropriate hepatic artery branch to the involved lobe, or (c) partial or complete lobectomy, and (2) location and external drainage of the liver cavity. Hypothermia is discussed as an adjunct to this type of surgery.

Courtesy of References and Reviews
Journal of the American Medical Association

Souliotis., P., Pettigrew, A., and Chamberlin, J.:
New Engl J Med 268:565 March 1963

GLUE SNIFFING

Over a period of about four and a half months 15 cases of "glue sniffing" were reported to this center. The authors discuss seven of these cases, occurring in five instances. Usually the patient reported that he was only one of a number of youngsters participating in the sessions. The increasing incidence of reported cases is apparently symptomatic of a growing fad, especially among teenagers, of inhaling the fumes of various types of plastic or airplane glues. Promoted either by word of mouth or press reports, the practice apparently consists of depositing the glue in a small paper bag which is held over the nose for a "sniffing session." The authors believe that the real significance of the practice lies not in the immediate physical effects (although in chronic usage serious damage is possible) but rather in its social aspects. The underlying factors which inspire youngsters to sniff glue for a "kick" may also lead to other and more damaging practices. Like alcoholism, drug addiction, use of ether, or gasoline inhalation, glue sniffing is not a disease entity but a symptom of basic emotional personality disorder.

The patients ranged in age from eleven to sixteen years; there were four boys and three girls. Five of the children had used airplane glue; one, plastic cement; and the other had sniffed a glue using a toluene solvent. Many are asymptomatic, but others have nausea, vomiting, and diarrhea. Some (such as the three girls in this series) report CNS depression or excitement, evidenced by giggling, dancing "feeling high," and other erratic behavior. Effects may include delirium and unconsciousness. Damage to blood-forming organs, kidney, and liver should also be considered.

While plastic glues have various formulas, a common type contains methyl isobutyl ketone 50 per cent and monomethyl ether or ethylene glycol acetate 50 per cent. The median lethal dose of each ingredient is 0.5 to 5 gm./kg. Maximum allowable concentration of methyl cellosolve is 25 parts per million. Among the plastic bases listed are polyvinylacetate, nitrocellulose, toluene, trichlorethylene, cyclohexanol, ethylenedichloride, and others.

Treatment is supportive and symptomatic. The authors add, however, that even though the patient may be asymptomatic, referral for psychiatric guidance may be indicated. Where use has been chronic, tests should be carried out to find whether or not there has been blood, kidney, or liver damage. Of the cases reported in this series, or in any of those reported to this poison control center, none apparently suffered any serious toxicity. As noted above the authors do not feel that this is the really important point. Glue sniffing, they say, is not an isolated event but a part of an over-all family and community health problem.

Courtesy of Medical Abstract Service
Berwyn, Illinois

Jacobziner, H., and Raybin, H.:
New York J Med 62:3294 October 15 1962

INTRA-ARTICULAR HYDROCORTISONE

Pursuant to reports by other investigators of radiographic deterioration of joints after the intra-articular injection of steroids over varying periods of time the authors add another case, that of a middle-aged patient who received 22 injections of hydrocortisone acetate in his knee over a period of twenty-seven months. X rays taken prior to surgery and compared with radiographs taken before cortisone therapy was started showed rapid deterioration of the joint, changes which were reflected symptomatically. At operation (a compression arthrodesis), marked destruction of the articular cartilage of tibiae and femoral condyles was found. There were multiple osteophytes and general fragmentation of cartilage. The menisci apparently were completely dissolved and there were synovial changes with about 10-15 cc. of clear but thick yellow fluid in the joint. The possibility that these Charcot-like changes may be related to the intra-articular use of steroids indicates the need for a more cautious approach to this type of therapy. Arthropathy of the Charcot type is thought to result from repeated trauma because of the individual's insensitivity to pain in the affected region. Although no true anesthetic effect of intra-articularly administered steroids has been demonstrated so far, the possibility of some direct chemical effect of these steroids in the articular cartilage should not be overlooked, the authors believe. Another possibility is that some shearing of the joint structures by the needle may be a factor, especially in the inexperienced hands. The authors suggest the advisability of limiting such injections to three or four over a period of a few weeks, followed by a period of more conservative management and careful observation of joints, especially the weight-bearing ones being injected. They should be watched for excessive effusion, ligamentous instability, and phenomena of a like nature.

Courtesy of Medical Abstract Service
Berwyn, Illinois

Steinberg, C., Duthie, R., and Piva, A.:
JAMA 181:851 September 8 1962

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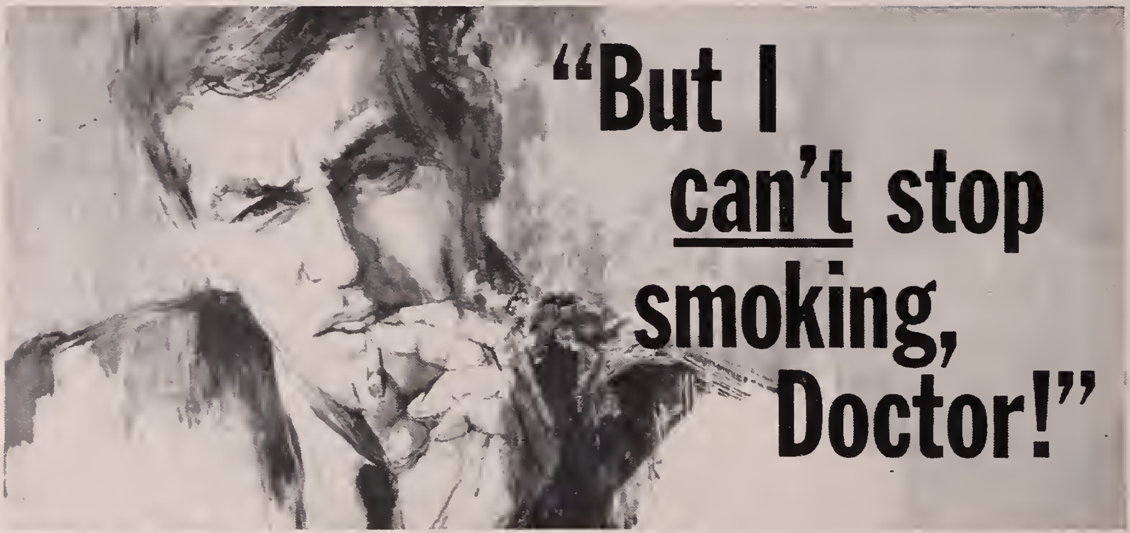
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References: 1. Goodman, L. S. and Gilman, A.: The Pharmacological Basis of Therapeutics, New York, Macmillan, 1960, Ed. 2, pp. 620-622; 2. Edmunds, C. W.: J. Pharmacol. and Exper. Therap., 1:27, 1909; 3. Hazard, R. and Savini, E. Gand., 92:471, 1963. 4. Dorsey, J. L.: Ann. Int. Med., 10:628, 1936; 5. Rasmussen, K. B.: Ugeskr.laeger, 118:222, 1956; 6. Ejrup, B.: Sven. lak. Tid., 53:2634, 1956; 7. Jochum, K. and Jost, F.: Munch. med. Wchnschr., 103:618, 1961; 8. Jost, F. and Jochum, K.: Med. Klin., 54:1049, 1959; 9. Smoking and Health, Summary and Report of the Royal College of Physicians of London on Smoking. New York, Pitman, 1962.

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BOOK REVIEWS

THE ELECTROCARDIOGRAM AND CHEST X RAY IN DISEASES OF THE HEART — Master, Lasser, Rosenfeld, and Donoso; Lea and Febiger, publishers, Philadelphia, 1963, 537 pages.

This book is neither a textbook of electrocardiography nor of cardiopulmonary radiology. Rather it supplements both disciplines with a "synthesis of the major diagnostic modalities." The initial pages deal with the normal, as delineated by the roentgenogram, fluoroscopy, and the electrocardiogram. The subjects of angiocardiography, vectorcardiography, and cardiac catheterization are virtually merely sketched in passing. Happily a fair amount of attention is given to the influence of age, body build, and respiration upon the X ray and electrocardiogram.

A valuable section dealing with cardiac chamber enlargement appears next.

The major portion of the book describes the findings in specific disorders, encompassing the whole spectrum of cardiac disease. The section on ischemic heart disease contains Dr. Master's most recent revision of his criteria for a positive exercise test.

The discussions of congenital heart disease are most attractive and call attention to the surprising amount of diagnostic information to be obtained via these rather mundane methods.

There are occasional statements that leave something to be desired, such as the explanation of the deep S V6 often seen in cases of left ventricular hypertrophy showing marked left axis deviation.

It could also be that too much is said about the time of onset of the intrinsicoid deflection as an indicator of increased muscle thickness in an era during which a string galvanometer has become nearly a museum piece.

Despite the above complaints which are minor, this book will be of interest to anyone who takes care of cardiac patients. It is rather easy to read and contains a multitude of excellent reproductions of chest X rays and electrocardiograms. For the student who wishes to study further there is a comprehensive bibliography adjacent to the appropriate topic.

Alan P. Rusterholz, M.D.
St. Paul, Minn.

SYNOPSIS OF EAR, NOSE, AND THROAT DISEASES — Ryan, Robert E., M.D., Thornell, William C., M.D., Von Leden, Hans, M.D.; C. V. Mosby Company, June 28, 1963. 425 pages. $7.50.

This up to date book on ear, nose and throat diseases is a useful reference for the busy practitioner. It is divided into four sections with fifty-eight chapters. A brief review of anatomy and physiology begins each section. The remaining chapters deal with specific disorders and summarize their etiology, pathology, symptomatology, prognosis and therapy. For common disorders, the symptoms and treatment are presented again in outline form at the end of the chapter. The book has a few illustrations which are adequate for this type of text.

In no way, does this book replace a good standard textbook in otolaryngology. A bibliography has been omitted. It is useful as a quick reference for those who wish to refresh their memory and review current accepted therapy in ear, nose and throat.

George V. Tangen, M.D.
Minneapolis, Minn.

CURRENT PRACTICE IN ORTHOPEDIC SURGERY IN 1963 — Editor, John P. Adams, Publication Date: 10/22/63, C. V. Mosby Co. Price $12.75

This book is a compilation of 10 separate monographs by different authors on various aspects of orthopedic surgery. The chapters on fingertip injury and trauma to the extensor mechanism of the distal phlanx concern subjects that will interest most practitioners. However, for the most part, the monographs in this issue are highly technical and will be of interest primarily to the orthopedic surgeon. Certain of the chapters are particularly well written, notably that on injuries to the menisci of the knee by O'Donoghue. The book is only 209 pages long and is not intended to cover the entire field of orthopedics.

Harrison H. Farley, M.D.
Minneapolis, Minnesota

Some books are to be tasted; others to be swallowed, and some few to be chewed and digested. — Bacon

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Special Articles

Cardiac Disease and Maternal Deaths in Minnesota*

DONALD W. FREEMAN, M.D.**
Minneapolis, Minn.

DISEASE INVOLVING the heart was diagnosed in 42 cases of maternal death studied by the Minnesota Maternal Mortality Committee during the 12-year period, 1950–62. In 10 of these cardiac disease was not the primary cause of death. Five patients with rheumatic heart disease died of the following conditions: pulmonary hemorrhage, pulmonary embolism, Asian influenza, amniotic-fluid embolism and poliomyelitis. One patient with a patent ductus arteriosus died of a subarachnoid hemorrhage two months postpartum. The other four cases included one of myocarditis with failure in association with a lymphoblastoma, one of toxic myocarditis with failure associated with an infected abortion and septicemia, one of congestive failure associated with disseminated lupus erythematosus, and one of myelogenous leukemia with leukemic infiltrations of the myocardium and endocardium.

The remainder of this paper will be concerned with the 32 deaths in which heart disease was considered the primary cause of death. These deaths accounted for 5.8% of all maternal deaths and for 9.7% of those due to obstetric causes. The deaths are listed by etiology in Table 1.

Four deaths caused by myocardial infarction and one due to rheumatic pancarditis were originally classified with the deaths due to nonobstetric causes and have been so listed in previous publications of the Minnesota Maternal Mortality Committee.[1]

TABLE I
Maternal Deaths in Minnesota Due to Cardiac Disease
1950-62

Type	No.	%
Rheumatic	12	38
Congenital	8	25
Myocardial infarction	6	19
Myocarditis	3	9
Hypertensive	2	6
Primary pulm. hypertension	1	3
Total	32	100

Results

Rheumatic Heart Disease

Six of the 12 patients had mitral stenosis, five had combined mitral and aortic disease,

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*Presented at John L. McKelvey 25th year Anniversary Celebration, Oct. 25, 1963.

**From the Minnesota Maternal Mortality Committee.

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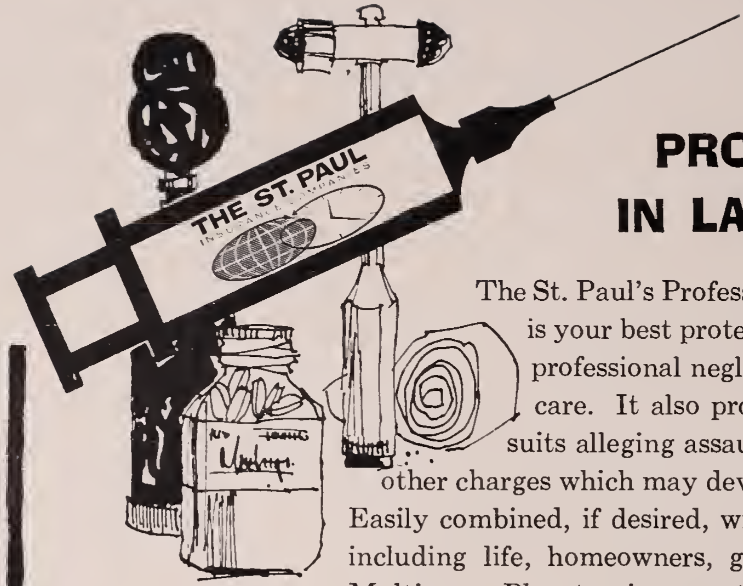
Continued



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and in one the type was unknown. The diagnosis was made at autopsy in six, and by clinical investigation in six. Four of the latter were thoroughly studied at a large teaching institution; another was evaluated by a qualified cardiologist between pregnancies; in the sixth case the pertinent data were reviewed after death by a cardiologist.

Two of the patients were primagravidas and the remainder multiparas.

One was age 18; six were in their 20s, three in their 30s; and two were over 40.

Of the six patients with mitral stenosis five died in failure. Two were undelivered at 27 weeks and 37 weeks gestation respectively, and three were postpartum. One of these died 12 hours after a radical cesarean section at term; another died two weeks postpartum after delivering at 36 weeks gestation; the third died nine days after delivery at 31 weeks gestation. The last-named patient also had subacute bacterial endocarditis, the only patient with this complication in the entire series. The sixth patient died suddenly 10 weeks postpartum.

Of the patients with combined mitral and aortic disease three died in failure as follows: one at 10 weeks gestation (her pregnancy was complicated at this point by chicken pox), one two days postpartum after being subjected to laparotomy for tubal ligation, and the third 12 weeks postpartum. The other two patients in this category died suddenly eight and 10 weeks postpartum respectively.

The patient with rheumatic heart disease of unknown type died suddenly one week after a late spontaneous abortion.

Thus, eight, or two-thirds, of the patients with rheumatic heart disease died of failure. Only three of these were still pregnant; but another four died within two weeks of delivery.

There were nine surviving infants delivered in this group.

Congenital Heart Disease

Five of these patients had interventricular septal defects; in two the diagnosis was patent ductus arteriosus, and one had a fistula between the aorta and the right ventricle. Of the patients with interventricular septal defects two were diagnosed at autopsy; two others had been diagnosed by cardiac catheterization. The diagnosis in the fifth case was made after all available data had been reviewed by a cardiologist. The diagnosis of patent ductus arteriosus was made in one case at autopsy and in the other at surgery; the aorta to right ventricle fistula was diagnosed at surgery.

Seven of the eight patients had either verified or probable pulmonary hypertension and showed cyanosis. Four were cyanotic prior to pregnancy.

Five of the patients were primagravidas and the others multiparas. All were in their 20s.

All of the patients with congenital heart disease died of cardiac failure. Of those with interventricular septal defects four died very rapidly with development of vasomotor collapse, marked aggravation of the cyanosis, and unconsciousness, within an hour of onset of the symptoms. Three of these were undelivered at 30, 31, and 33 weeks respectively, one of them in labor. The fourth death occurred seven hours after delivery at 39 weeks gestation. The last patient with an IV septal defect died in failure in association with excessive vaginal bleeding two weeks after a late spontaneous abortion.

One of the patients with a patent ductus died of failure one week postpartum after delivering at 32 weeks gestation, her condition complicated by acute glomerulonephritis. The other, who also had pulmonary hypertension and a reversed shunt, died immediately after the ductus was ligated some two and a half months postpartum. The patient with the aorta to right ventricle fistula died in failure 30 hours after a therapeutic abortion, performed by subtotal hysterectomy at 10 weeks gestation.

Three infants survived in this group.

Coronary Heart Disease

Five of the six cases in this group were diagnosed at autopsy and the other by typical history, and by physical and electrocardiographic changes. All had myocardial infarctions. None had had infarctions prior to this pregnancy nor were any known to have

Continued

The discharged mental patient . . . and Thorazine®

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"The average practitioner is quite capable of handling the vast majority of ex-institutionalized patients by regulation of medication, reassurance, manipulation of the environment where necessary, and . . . other technics." Kline, N.S.: Postgrad. Med. 27:620 (May) 1960.

The family physician must often assume responsibility for the discharged mental patient. Thorazine (chlorpromazine, SK&F) can be a valuable adjunct to the continuing care of this patient, because it helps prevent relapses by insulating him from the impact of stressful experiences. For successful rehabilitation and prevention of rehospitalization, however, the former mental patient—and often his family—also needs the guidance and counsel of his physician.

Many physicians are surprised by the high doses of Thorazine (chlorpromazine, SK&F) used in patients released to their care from mental hospitals. This surprise may be expressed by a drastic reduction in dosage "to play it safe"—with serious consequences for the patient.

The successful maintenance of former mental patients requires adequate, often "high" dosage, and often for prolonged periods of time. Fortunately, these dosages do not mean greater risks for the patient. On the contrary, there is much less risk of serious side effects once a patient has become gradually accustomed to Thorazine (chlorpromazine, SK&F)—*regardless of dosage*—over a period of a few months. Continuing therapy is almost always well tolerated, and is essential to most patients' continued well-being.

Brief Summary: Thorazine (chlorpromazine, SK&F) has been successfully used for 10 years in the treatment of mental and emotional disturbances, and has proven highly effective in the maintenance therapy of former hospitalized mental patients. *Principal side effects:* The most frequently encountered side effect is transitory drowsiness. Other occasional side effects include: dry mouth, nasal congestion, constipation, miosis, dermatological reactions, photosensitivity, jaundice, hypotension, increased appetite and weight; very rarely, mydriasis, agranulocytosis, extrapyramidal symptoms. *Contraindications:* Comatose states or in the presence of excessive amounts of C.N.S. depressants.

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coronary heart disease antepartum. The etiology in one was periarteritis nodosa.

The age range was from 31 to 41. All were multiparas.

Two of the patients died suddenly at the time of their infarctions, three and 10 days postpartum respectively. In the other four cases the infarctions occurred in close association with labor. One of these patients suffered two infarctions, the second of these occurring three days before the onset of labor. In two others infarctions occurred during labor, and in the final case 36 hours before the onset of labor. It was striking to note how poorly labor was tolerated in these four patients. Death occurred during labor in one, six hours postpartum in two, and 31 hours after delivery in the fourth.

Five infants from this group survived.

Myocarditis

The etiology in two of these three cases was considered to be rheumatic fever; the other was possibly rheumatic as well. Two of the patients had pancarditis with endocarditis and pericarditis associated with the myocarditis. One was diagnosed at autopsy and the others by typical history and by physical, electrocardiographic, and X-ray findings.

Two died in failure, one of these undelivered at 20 weeks gestation, and the other 20 hours after delivery at 34 weeks gestation. The third patient died suddenly five and a half weeks postpartum.

One of these patients was a primagravida, the others multiparas. Two were age 22 and the other 23.

Both delivered infants survived.

Others

The two patients with hypertensive heart disease were diagnosed by typical history and physical findings; the case of primary pulmonary hypertension was diagnosed at autopsy.

One patient was a primipara, the others multiparas. The hypertensive patients were aged 33 and 40, the patient with pulmonary hypertension, 36.

All of these patients died of failure. Death occurred in one with hypertensive heart disease at 10½ weeks gestation and in the others at two and three months postpartum.

Both delivered infants survived.

Discussion

The outstanding change from previous reports is the drop in proportion of deaths in Minnesota due to rheumatic disease and to bacterial endocarditis, with an increase in the role played by congenital and coronary heart disease. Other reports have shown that rheumatic heart disease accounted for 75% or more of cardiac deaths among pregnant women with bacterial endocarditis, accounting for about 10%. Congenital heart disease was responsible for less than 5%, and deaths from myocardial infarctions were even more unusual.[2,3]

The decline in the rheumatic heart disease deaths probably is a reflection, in part, of better care. However, there has been a general decline throughout the United States in the mortality rate from rheumatic fever and rheumatic heart disease.[4] This decline has been more rapid since the introduction of chemotherapy for treatment of streptococcal infections and the prevention of recurrent attacks of rheumatic fever by prophylactic treatment. In this connection it is noteworthy that there was only a single case of endocarditis in the Minnesota series. A continuing decline of maternal deaths due to rheumatic disease may be safely predicted. Recent prevalence data indicate that at present less than two per 1,000 elementary school children are affected with the disease, compared with a prevalence of 16 to 18 per 1,000 found in World War II Selective Service registrants. The same studies indicate that congenital heart disease may actually be more prevalent than rheumatic disease among elementary school children in the United States today.[4] However, one may also expect fewer obstetric deaths from congenital heart disease in the future, due to advances in surgical technique together with better efforts at early case finding.

Obstetrical Care and Preventability of Deaths From Heart Disease

It has been sugggested that ideal care should make virtually all deaths from rheumatic heart disease during pregnancy pre-

Continued

ventable.[5] On the other hand, Mendelson feels that pregnancy produces a sufficient load on the heart to cause death in some cases despite completely adequate care. He has reported that such deaths have occurred from failure generally at the time of the peak "pregnancy load."

Only six of the Minnesota Maternal deaths were considered by the Committee to be preventable. However, in assessing preventability ideal care is usually not expected, and in this series it was rarely applied. Nevertheless, in 11 cases care which could not be criticized was given patients who died during the time of increased cardiac load either during pregnancy or within a week of delivery. It must be considered that in at least some of these cases pregnancy brought about death earlier than would the natural course of the patient's disease. Seven of the 11 died of cardiac failure, and four deaths due to myocardial infarction occurred in close association with the increased effort involved with labor and/or delivery. The practical question one may then ask is: "How many of these 11 deaths might have been prevented had pregnancy been avoided or had therapeutic abortion been carried out early in the pregnancy?" In eight of the 11 cases the question would not have been applicable. Cardiac disease was not evident in two patients with myocarditis, or in four who died of myocardial infarction, until late in pregnancy. Unforeseeable complications were factors in two other deaths. Three cases remain. All of these patients had interventricular septal defects with evidence of pulmonary hypertension and right to left shunt; all died undelivered at the time of the peak "pregnancy load" at 30, 31 and 33 weeks gestation respectively. Death was attributed in each to acute right ventricular failure.

Vascular Collapse, Sudden Death and Congenital Cardiac Disease

Cases of sudden vascular collapse with aggravation of cyanosis, unconsciousness, and sometimes death have been described previously in obstetric patients with aberrant communications between the heart chambers or the great vessels. These have occurred immediately postpartum and have been generally attributed to a drop in peripheral resistance, with production of or aggravation of a right to left shunt through the communication.[3,6,7] This type of very rapid collapse and death occurred in five patients with congenital heart disease in this series. In one patient with an interventricular septal defect this occurred immediately postpartum; but an identical picture was seen in the three undelivered patients referred to above and in another after ligation of a patent ductus postpartum.

Physiologic Mechanism

In the usual course of events, in patients with this type of aberrant communication, a gradual rise in pulmonary resistance occurs, resulting in a lowering of the amount of blood shifted from left to right through the shunt. For a time the amount shifted in each direction may be equal, and when pulmonary resistance reaches a level which exceeds the peripheral pressure, a right to left or "reversed" shunt occurs. The reversing of the shunt actually serves as a protective mechanism for the right ventricle by halting the pressure rise against which it must work. At the same time the high pulmonary pressure reduces the pulmonary blood flow and so lessens the cardiac burden. Thus, the reversed shunt is not of itself harmful. Indeed, should this "safety valve" be shut off, as occurred in the case of the patient subjected to ligation of the ductus, acute failure can occur, because the right ventricle cannot tolerate working against the greatly increased pressure. However, even when the shunt is functioning, the balance in these situations is always precarious. The right ventricle has a very limited ability to increase its output. Attacks of syncope with effort are known to occur in patients with pulmonary hypertension. These have been shown to be due to acute failure of the right ventricle.[8] It seems likely then that the increasing cardiac load of pregnancy and/or delivery can similarly result in acute failure in these patients. It is considered significant that all four patients with interventricular septal defects in this group had signs suggestive of incipient failure for from four days to three weeks before death occurred in the fulminant manner described. These signs included increased fatigue, "dizzy" spells, faint feelings, and an increase in cyanosis.

Summary

1. Thirty-two maternal deaths due primarily to cardiac disease occurred in Minnesota in the years 1950–62. They accounted for 5.8% of all maternal deaths and for 9.7% of those due to obstetric causes.
2. Eight of 12 deaths due to rheumatic heart disease resulted from cardiac failure. Seven of the eight occurred during pregnancy or within two weeks of delivery. One of these patients also had subacute bacterial endocarditis, the only case in the series.
3. All eight deaths due to congenital heart disease occurred in patients who had aberrant communications between the right and left circulations. Seven of the eight showed cyanosis and had verified or probable pulmonary hypertension. All eight died of cardiac failure.
4. Four of six deaths due to myocardial infarction occurred in close association with labor. None of the six patients was known to have coronary artery disease prior to the pregnancy.
5. Three deaths were due to myocarditis, two to hypertensive heart disease and one to primary pulmonary hypertension. Three of five deaths from cardiac failure in this group occurred during pregnancy or within 24 hours of delivery.
6. Six of the maternal deaths were considered preventable. Of the patients who died during a time of increased cardiac load due to pregnancy effects, 11 were given adequate care with respect to their cardiac condition.
7. The over-all fetal survival was 66%.

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—N. E. A. Journal

Habits are cobwebs at first; cables at last. — Chinese Proverb

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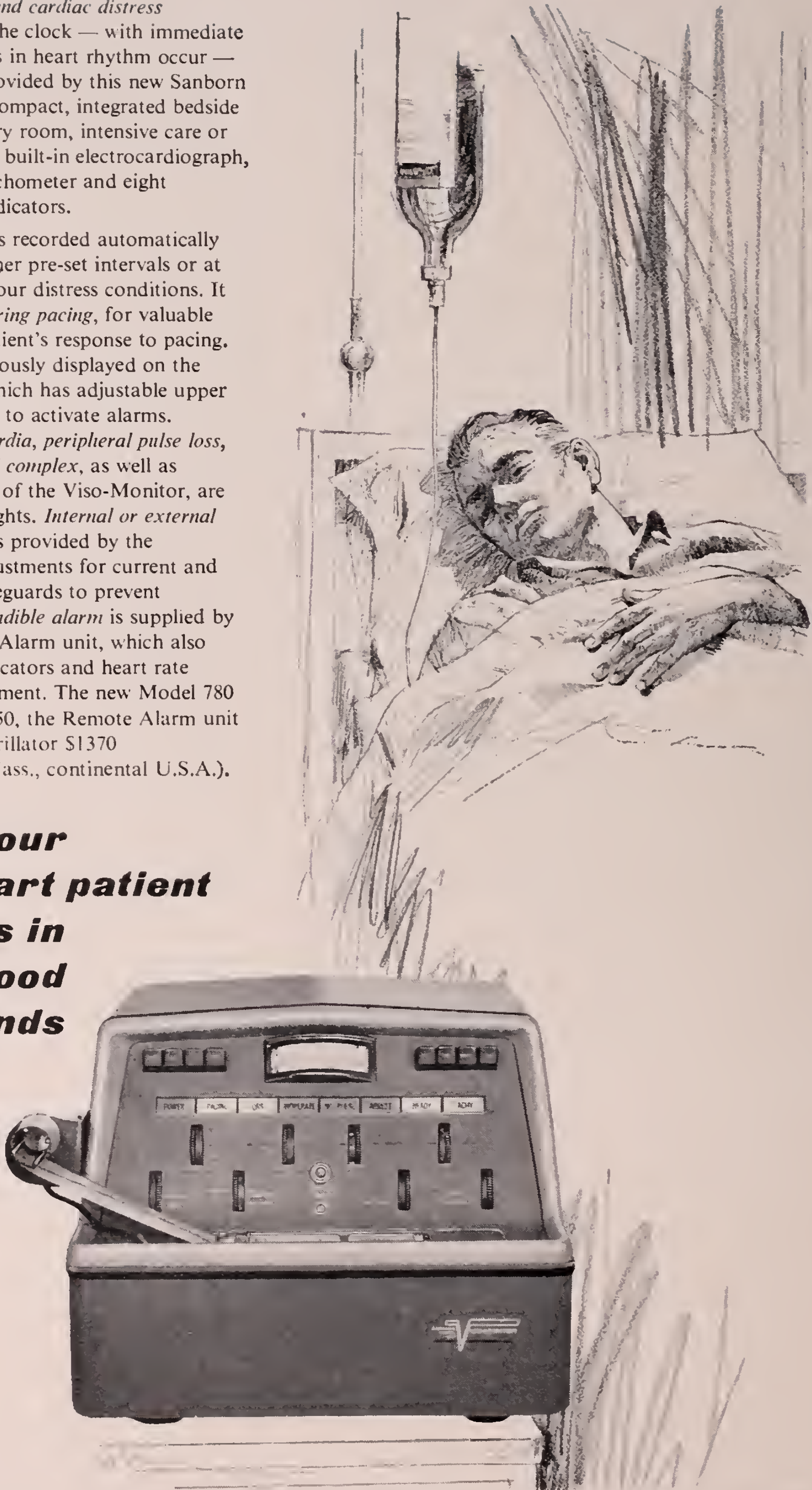

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Meetings And Announcements

FEBRUARY

University of Texas postgraduate course in Dermal Pathology, February 17-21, Texas Medical Center, Houston, Texas. Contact: J. Leslie Smith, Jr., M.D.; 102 Jesse Jones Library Building; Houston.

American College of Allergists, Americana Hotel, Bal Harbour, Fla., February 29-March 6. Exec Sec: E. Bauers, 2160 Rand Tower, Minneapolis 2.

American College of Surgeons (sectional meeting), Denver-Hilton Hotel, Denver, February 17-19. Sec: Samuel P. Harbison, M.D., 55 E. Erie, Chicago 11.

Central Surgical Association, Rochester, Minn., February 27-29. Sec: Carl E. Lischer, M.D., 457 N. Kingshighway, St. Louis 8.

International Academy of Proctology Teaching Seminar, Deauville Hotel, Miami Beach, Fla., February 29-March 5. Info: A. J. Cantor, M.D., 147-41 Sanford Ave., Flushing 55, N. Y.

MARCH

Twenty-seventh annual meeting of The New Orleans Graduate Medical Assembly, March 2-5, Roosevelt Hotel, New Orleans, La. Contact: Office of the Assembly; 1430 Tulane Avenue; New Orleans, La.

Mayo Clinic Clinical Reviews, March 16-18 and 23-25 in the Mayo Civic Auditorium; Rochester, Minnesota. Contact: M. G. Brataas; Mayo Clinic; Rochester.

Department of Otolaryngology, University of Illinois, postgraduate course in laryngology and bronchoesophagology, March 16-28, Chicago. Contact: University of Illinois College of Medicine; 1853 West Polk Street; Chicago.

American College of Surgeons tenth annual meeting in New Orleans, March 16-19, Roosevelt Hotel. Contact: American College of Surgeons; 55 East Erie Street; Chicago.

17th National Rural Health Conference of AMA to be held at the Columbus Plaza Motor Hotel, Columbus, Ohio, March 6-7. Contact: AMA, Chicago.

University of Colorado School of Medicine postgraduate course in medical technology, March 16-21 in Denver, Colorado. Contact: University; 4200 East 9th Avenue; Denver, Colorado.

ANNOUNCEMENTS

Applications are now being accepted for the E. V. Allen Memorial Scholarship. Predoctoral and postdoctoral students interested in three months' cardiovascular study at the Mayo Clinic may obtain information from the Minnesota Heart Association, 1821 University Avenue, St. Paul, Minn.

* * *

The next scheduled examination (Part II), oral and clinical, by the American Obstet. & Gyn. Board will be conducted for all candidates at the Edgewater Beach Hotel, Chicago, Illinois by the entire Board, April 27-May 2. Candidates will be sent notice of examination dates.

* * *

University of Minnesota Continuation Medical Courses.

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April 3-4	Trauma
April 23-25	Gynecology

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No Need for King-Anderson Minnesota State Medical Association Reveals

Nine days of scheduled House Ways and Means Committee hearings on the King-Anderson Bill H.R. 3920 were interrupted on the fifth day with the assassination of John F. Kennedy, Friday, November 22, 1963.

The hearings have produced a barrage of oral and written testimony which show that King-Anderson type legislation is unnecessary.

Following is a partial statement submitted for the record on behalf of the physicians of Minnesota. This new statement based on more recent studies and available information augmented by the statement two years ago, demonstrates conclusively that there is absolutely no need for a social security financed eldercare legislation in Minnesota.

The legislature in Minnesota has now passed a comprehensive medical care program under the Medical Assistance to the Aged portion of the Kerr-Mills bill which will take care of such needs. The state has had a full benefit Old Age Assistance program, in addition, for the past fifteen years.

The M.A.A. plan will provide full health care benefits for 38% of all the senior citizens.

Over 140,000 of the 367,071 persons over 65 in Minnesota will receive $13,700,000 in additional health benefits each year. Those who qualify will be able to own and keep up to:

1. $15,000 in real property
2. $1,800 annual income if single and $2,400 if married
3. $750 liquid assets if single, and $1,000 if married. Not included are personal and household effects, prepaid burial plot, or cash surrender value of each person's life insurance up to $1,000. This latter provision may be waived by the county agency administering the plan.

The above named benefits are available to the recipient after he has paid the first $200 of his health care bills in the preceding twelve month period. Health insurance premiums are included in the $200 deductible, and the insurance benefits are applied to the health care costs of the individual beneficiary before the remainder of his bill is paid by the administering agency. Again, the agency may waive the $200 deductible if it causes undue hardship on the recipient. The Minnesota M.A.A. plan will become effective July 1, 1964.

Minnesota Blue Cross began selling two new health plans tailored exclusively for senior citizens over age 60 in January, 1963. The first, known as Series Sixty Plan A, is a $25.00 deductible program which pays

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Plan B of the Sixty Series is a 75-25 co-insurance plan entitling the subscriber to 70 days of hospitalization every six months. All hospital services enumerated above are covered as well as daily room and board in a two or more bed room. Out-patient care is covered if the patient is admitted to the hospital within 24 hours after the accident. Non-acute care is covered if the patient enters such a facility within 72 hours after discharge from a confinement of at least 5 days or more in an acute hospital. The premium for this plan is $150.00 a year.

Minnesota Blue Cross has always provided coverage to all persons through group plans or individual contracts when enrollment occurred before the age of 60. Individual contracts are guaranteed renewable beyond the age of 60.

More than 65,000 Minnesotans are covered by the two Sixty Series plans and the 80-20 co-insurance plan provided for group contract retirees. There are many more thousands over age 65 who are still working and covered by group contracts.

The basic senior citizens contract of Minnesota Blue Shield is beginning its third year of operation. It has had fine acceptance in the state. Over 8,978 have subscribed to the senior citizens contract.

Blue Shield's new service plan provides for comprehensive benefits for all individuals over age 65 whose income is $2,400 or less and couples whose income is less than $3,600 annually. An individual's net worth may be $20,000 or less and couple's $30,000. The plan costs only $35.40 a year.

Blue Shield has a hospital expense rider plan for senior citizens, but few have taken advantage of it. The plan is very reasonable and provides excellent benefits. The aged person can purchase a non-deductible, or $50.00, or a $100.00 deductible policy. He may secure from 30 to 120 days of hospitalization coverage in a 12 month period with a maximum room allowance of $10, $12, $15, or $20 per day. The premiums range from $4.70 to $11.75 a month. Over 2,600 aged persons are covered under this plan.

Hence, Blue Shield and its hospital rider plan can provide full-service physician benefits, as well as 120 days of hospital care, at $20,000 per day for $176.40 a year. Nearly 79,000 persons in Minnesota over 65 have a Blue Shield contract.

The Taves Senior Citizens Report noted in 1960 that 60% of the persons interviewed had hospital insurance and that in the metropolitan area where hospital costs are much higher, 71% had such coverage. Over 50% had medical and surgical coverage. It should be noted that this survey was done before the Blue Shield and Blue Cross plans mentioned above were available.

Minnesota's Old Age Assistance program is one of the best in the nation. In the fiscal year ending June 30, 1962, $26,821,810 was spent on medical care for Minnesota's old age assistance recipients. Hospital and physician costs continued to decrease while nursing home costs have increased.

Old Age Assistance recipients in Minnesota received comprehensive benefits and have free choice of vendor. In 1963, 42,700 persons over age 65 are receiving aid under this program. Almost 57% receive medical care at some time during the year, and 52% of the total money spent for Old Age Assistance will be for health care.

Hence, in Minnesota, the senior citizen can purchase excellent health care coverage at nominal rates, and those who cannot afford such rates can receive comprehensive care under the Old Age Assistance or the new Minnesota Assistance to the Aged programs.

In the current population report of the United States Department of Commerce, Bureau of Census, it is pointed out that 91.8% of the families whose head was 65 or over had an income of over $1,000. In fact 27.7% had incomes over $5,000. The

Continued

median income of these families was $3,382 annually.

The November 1960 Monthly Labor Review states that an adequate budget for a retired couple in Minneapolis in the Autumn of 1959 was $3,135.00. This would indicate that aged Minnesotans who receive the national median income of $3,382 would have more than enough to live on. Included in the retired couple's budget mentioned above was $315.00 for health expenses. The Hennepin County Welfare Department figures a minimum budget is $1,854 annually for a couple.

How Do Minnesotans Pay for Hospital Bills

A study has been made over the last three years of hospitalized patients in a rural Minnesota hospital. This hospital has 41 beds and 10 bassinets. Of the total admissions during the three years, 17.7% were over 65 years old and of that group, 14.1% were admitted for surgical operations and 85.9% for medical conditions.

Three-quarters of the patients over 65 paid their bills from private resources, including insurance payments, and one-fourth of the bills were paid by government programs. Each year the number of persons who had all or part of their hospital bill paid by insurance has increased. In 1960, 33% of the aged had insurance coverage. By 1961, the percentage increased to 40% and in 1962 over 46% had coverage. In the first six months of 1963, 51% secured insurance benefits.

During the three year period, 84.9% of all persons hospitalized over 65 received bills that were under $500 and only 5.3% spent over $1,000.

The most important point in this study, as it relates to the King-Anderson bill, is that by February 15 of each ensuing year only 3.5% or 11 people had not paid their hospital bills in full. Just a little over 1.4% or 4 people in the group had not made any payment at all on the account.

A 1963 Twin City hospital study pointed to the fact that older people pay their hospital bills faster than any other age group. The study, which included 11,029 discharges from the 25 short-term general hospitals, was a 5% probability sample. "Grandma and Grandpa — at whatever age 50 and above you choose — are the lowest nonpayers of their bills in both percentage by number and percentage by amount," the report stated.

The age group of 20-29 accounted for the largest group of persons who did not pay their hospital bills. Over 6.71% of old bills charges from this group remained unpaid at least six months after discharge. In addition, their average bill is one of the lowest for any age group.

The Hennepin County Community Council's 1963 survey revealed that in a sixty day period, 17% of new admissions for all clinic services at the Minneapolis General Hospital were for persons 65 years and over. This would indicate that over 80% of the charity and emergency cases in Hennepin County involved younger persons.

All these studies show clearly that senior citizens in Minnesota can and do pay their hospital bills. Two of the studies indicate that younger couples seem to have a more difficult time paying these bills. Yet under the King-Anderson bill, the government will tax the young couple and provide "free" health service to the aged. It is obvious that most older people do have the means to care for themselves and they want to do so.

Comparing the Minnesota Medical Assistance Law with the King-Anderson Bill

1. *Who would be covered?* Under the Minnesota Assistance to the Aged program, 140,000 persons over 65 will receive comprehensive health services. The King-Anderson bill will provide institutional health benefits to 367,000 or nearly all of Minnesota's aged.
2. *What benefits would the people receive?* After a small deductible, the King-Anderson benefits provide for the first 45, 90, or 180 days of hospital care in a benefit period. What happens to the patient who has an acute condition and uses up the 45, 90, or 180 days? If he doesn't have the money to pay for the health care, he must seek relief.
   The Minnesota Assistance to the Aged plan asks the recipient to pay the first

$200 of health care in any twelve-month period and after that, all remaining health care is paid in full. This is set up as a "catastrophic" plan, because this is the type of health care insurance the aged need.

The Hennepin County study revealed the fact that persons over 65 do not get proper dental care. The King-Anderson bill does not help persons over 65 to secure dental care. On the other hand, the Minnesota Medical Assistance plan provides complete dental care after the $200 deductible for all health care. Hence we must point out that the Minnesota Assistance to the Aged bill will do the best job in caring for the health needs of the people over 65.

3. *Is it necessary to provide some health care to all the aged in Minnesota?* We noted earlier that only 5% of the Minnesota aged stated they needed health care and did not have it because they could not pay for it. The same study noted that 49% of the people said they had enough money on which to live comfortably and over 50% had $10,000 net worth or more. The people of Minnesota are already providing complete health care to 12% of the aged population and now going to make the same benefits available to 38%. We know that another 21% are covered by Blue Cross and Blue Shield, and that more than 50% of the aged in Minnesota can afford to buy health insurance because they have done so. The doctors of Minnesota feel that most of Minnesota's aged population can afford to buy insurance or they have already bought insurance and can use it to pay for their health care.
4. *What government controls are placed on the doctor under both plans?* Under the King-Anderson bill, the Secretary of Health, Education and Welfare or his assistants, sitting in Washington, D.C., or at regional offices, will administer the plan. In many cases they will not know the differences that exist in health care practices from county to county and state to state.

The individual doctor will be in constant jeopardy because the hospital utilization committee can force him to move his patient whether or not he feels it is in the best interest of the patient. If the hospital in which the doctor practices does not sign an agreement with the government, the doctor cannot take his aged patients to that hospital unless the patient abrogates his right for "free" care in order to choose his own physician. The doctor cannot prescribe a new drug and have it paid for unless it is found in one of the four drug encyclopedias or approved by the local drug committee.

The Minnesota Assistance to the Aged plan is administered by the county welfare departments. Each patient is free to choose any doctor, hospital, or nursing home. The physicians, through the medical society, have agreed to service the Minnesota Assistance to the Aged plan at Blue Shield Plan "A" rates. Each local medical society has established a committee to review any questionable charges for the local welfare department, and the physicians have agreed to this procedure. The same type of structure has been established for the dentists and pharmacists, but hospitals and nursing homes receive full payment for their services. The doctor is free to treat the patient without government interference.

5. *Where will we find the personnel to care for all of the people who are sure to take advantage of "free care"?* One of the problems that would confront this country immediately if 17 million persons over 65 demanded their "right" for "free" health care would involve lack of the personnel to care for them. The Hennepin County study noted that. "A shortage of professionally trained people in the medical and paramedical fields, including social services and research, still remains as bottlenecks for the development of expanding health services in Minnesota and in Hennepin County."

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6. *What are the costs of the two plans?* The total cost for providing complete care for 140,000 aged Minnesotans under the M.A.A. plan would be estimated at $13,700,000 a year. Of this amount, Minnesotans will pay about $2 million a year, plus Minnesota's percentage of the $11.7 million which will come from federal funds. One fiftieth of $11.7 million is $234,000. We realize that $234,000 is only an estimate, but it is safe to predict that the total cost would be about $2,234,000 a year in new taxes. On the other hand, we know that the people of Minnesota will pay at least $19,180,000 in additional Social Security taxes each year for the King-Anderson bill. In 1962, 1.4 million people in Minnesota paid social security taxes. The average annual wage on which the Social Security tax was levied was $2,740.00. To finance the King-Anderson plan, Social Security taxes would be raised ¼ of 1% on the employer and ¼ of 1% on the employee or ½ of 1% overall. One-half of 1% of $2,740 is $13.70, the average tax increase per individual. Multiply this figure by the 1.4 million who pay this average tax increase, and $19,180,000.00 is what Minnesotans will pay to the federal government for partial institutional care for all persons over 65, whether or not they can pay for their own care.

No Need

In view of the factual material presented in this testimony, it is abundantly clear that there is no need for the King-Anderson program in Minnesota. We feel that within one year all persons in Minnesota over 65 will have the finest health care available, and they will not need to be impoverished to get such care. The doctors in our state feel that this is the way it should be. Older people should not be made class 1, class 2, or class 3 citizens. They should be able to keep some resources, and yet when they need health care, they should be able to get all of the care they need. All studies point to the fact that those who can afford health insurance are buying it. Nearly everybody wants to be self sufficient. They do not want the government deciding whether or not they have stayed in the hospital too long. The fact is, our programs are so good in Minnesota that we do not want the federal government to come in and take more of our tax dollars to give us less service than we now receive.

Summary

The truth is, as we have noted before, that we physicians helped to create the problems of the aged, and we feel we can help to eliminate them. Our sole interest lies in helping our aged patients to receive the best possible medical care.

We firmly believe that the numerous controls placed on the physician, the contracts that must be signed by the hospitals, the qualifications that nursing homes have to meet, the limited benefits of the program, and the fact that the King-Anderson bill is not flexible enough for the needs of the aged, will all work to the detriment of our patients, our own mothers and fathers, and our grandparents.

We are confident that, beginning July 1, 1964, we will have no problems in Minnesota. All of our aged will be able to pay their health care bills through use of the MAA program, their private resources, or by the private insurance companies. We know that this is the way people want it. Elderly people are not looking for "something for nothing." They have said it time and time again. They want to pay for their care if they can. If they cannot pay, then we in Minnesota feel that complete care must be provided for them, for as long as they need it. No one will ever again be forced into indigency because of health care bills in our state. The state of Minnesota has taken care of this responsibility to our aged population.

We continue to be unalterably opposed to the King-Anderson approach, and we will use all of our resources to develop our Minnesota plan for giving full assistance to those who need help, and for helping all others to help themselves.

One is easily fooled by that which one loves — Moliere-Tartuffe

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Special Report

Portland—1963

AMA Clinical Meeting Actions Reviewed

Following is the official summary, supplied by the American Medical Association, of the actions taken by its House of Delegates at the seventeenth clinical meeting.

Tobacco and health, the rights and privileges of Negro physicians, revision of the AMA Constitution and Bylaws, voluntary health agencies and blood banks were among the major subjects acted upon by the House of Delegates at the American Medical Association's Seventeenth Clinical Meeting held December 1-4 in Portland, Oregon.

The House at its opening session expressed deep shock at the tragic death of the late President John F. Kennedy and directed that a letter of heartfelt sympathy be sent to Mrs. Kennedy, her children and the late President's family. The House also pledged its support to President Lyndon B. Johnson in forging national unity in the weeks and months ahead and offered the Association's resources, counsel and cooperation on matters of health.

Doctor Edward R. Annis, AMA president, reporting on the recent House Ways and Means Committee hearings on the King-Anderson Bill, told the House:

> "The combined testimony of the American Medical Association, the state societies and our allies made a far greater impact on the members of the committee, friend and foe alike, than at any other time in the history of this long and bitter conflict."

Doctor Annis also reported that under questioning from Committee Chairman Wilbur Mills, actuaries of the Department of Health, Education and Welfare admitted that the program of tax-paid hospitalization and related benefits for the aged proposed in the King-Anderson Bill would require a tax rate twice as high as they have previously claimed.

Final registration at the Portland meeting reached a total of 7,103, including 3,144 physicians.

Tobacco and Health

The House approved a Board of Trustees proposal that the American Medical Association Education and Research Foundation undertake a "comprehensive program of research on tobacco and health."

Agreeing that many gaps exist in knowledge about the relationship between smoking and health, the House declared that the study should be "devoted primarily to determining which significant human ailments may be caused or aggravated by smoking, how they may be caused, the particular element or elements in smoke that may be the causal or aggravating agent, and methods for the elimination of such agent."

The action called for procuring a project director "whose experience, qualifications and integrity will assure that such a research project will be conducted effectively, exhaustively and with complete objectivity."

The House agreed that the project should be financed by a substantial contribution from the American Medical Association and that contributions should be solicited from other sources—industry, foundations, voluntary health agencies and physicians. It was emphasized that contributions will be accepted only if they are given without restrictions.

Subsequent to the House action, the AMA Board of Trustees voted to contribute $500,000 to help finance the research program.

Continued

Negro Physicians

The House considered two proposals related to Negro physicians—a Board report on hospital staff privileges and a resolution concerning membership eligibility in state and county medical societies. The Board report was approved, but the resolution was not adopted.

In adopting the Board report, the House declared that "members of the medical staff of every hospital, where the admission of physicians to hospital staff privileges is subject to restrictive policies and practices based on race, be urged to study this question in the light of prevailing conditions with a view to taking such steps as they may elect to the end that all men and women professionally and ethically qualified shall be eligible for admission to hospital staff privileges on an equal basis, regardless of race."

In both its approval of the Board report and its rejection of the proposed resolution—which would have denied the rights and privileges of AMA membership to members of any state or county society which refuses membership to any qualified physician because of race, religion or place of national origin—the House reaffirmed 1950 and 1952 policy actions on this subject and directed that a copy of the 1950 resolution again be sent to each state and county medical society. That resolution urged that "constituent and component societies having restrictive membership provisions based on race study this question in the light of prevailing conditions with a view to taking such steps as they may elect to eliminate such restrictive provisions."

AMA Constitution and Bylaws

The House approved comprehensive revisions and rearrangements of the Association's constitution and bylaws as submitted by the Council on Constitution and Bylaws. Among the changes are the following:

1. The Annual and Clinical "Sessions" have been renamed the Annual and Clinical "Conventions."
2. The word "constituent" has been changed to "state."
3. Two types of membership have been created, "Active" and "Special." Active Members are Regular or Service Members. Special Members are Associate, Affiliate and Honorary Members.
4. Affiliate Membership will be available to American physicians engaged in medical missionary and similar educational and philanthropic labors located in possessions of the United States.
5. A quorum will be 100 of the voting members of the House rather than 75.
6. A method has been established to replace a general officer who misses six consecutive meetings of the Board of Trustees.
7. A method has been established for the successor to the President to assume the Office of President if the President dies, resigns or is removed from office.
8. The Board of Trustees has been given express authority to appoint committees.

The House retained present provisions concerning voting on amendments to the constitution but agreed that this matter might be considered by the Committee to Review the Organization of the AMA House of Delegates.

Voluntary Health Agencies

In approving a Board report on professional relationships with voluntary health agencies, the House declared that "the AMA maintain its policy of neither approving nor disapproving national voluntary health agencies." It also agreed "that the AMA, through its Committee on Voluntary Health Agencies, maintain its position of offering guidance on medical aspects of national voluntary health agency programs."

The House approved the "Principles for Medical Guidance to National Voluntary Health Agencies" which contain a new definition of a voluntary health agency, objectives of the Committee on Voluntary Health Agencies and a list of suggested mutual obligations between the AMA and the national voluntary health agencies. The House directed attention to the following two obligations:

"There should be a mutual exchange of information and opinion enabling the medical profession and the agency to understand each other's policy and practice."

"A national voluntary health agency should seek the advice of the medical profession when embarking on a national medical program."

In another action, the House also agreed with a recommendation that the Committee on Voluntary Health Agencies be given the status of a council in the AMA organizational structure.

Blood Banks

The House adopted a policy statement pointing out that in recent years there has been a dramatic growth of blood banking facilities in the United States and declaring that "it is highly essential that the organization of new blood banking programs and the modification of existing ones should have, in the interest of public health and safety, the approval of the county or district medical society and, therefore, should be coordinated with existing approved blood banking facilities." The House also approved a floor amendment stating that since a blood bank can well be considered a medical facility, the top authority in a blood bank should be a physician.

Miscellaneous Actions

In considering a wide variety of reports and resolutions, the House also:

Changed the name of the Council on Scientific Assembly to the *Council on Postgraduate Programs;*

Extended AMA Affiliate Membership to scientists in sciences allied to medicine;

Changed the name of the Council on Medical Education and Hospitals to the *Council on Medical Education;*

Approved an amendment to the Bylaws which would permit the opening session of the House of Delegates to be held on Sunday afternoon or evening;

Expressed gratification that the work of the Committee on Medicine and Religion has received widespread acceptance and support from state and county medical societies, religious groups and other related organizations;

Received a report on the AMA Members Retirement Plan and urged physicians to act quickly if they are to exercise their rights under Public Law 87-792 during 1963;

Requested the AMA to seek improvements in the format of its American Medical Directory to make it easier to use;

Asked the Association staff to study the feasibility of opening the Clinical Meeting two Sundays prior to Thanksgiving Day;

Approved recommendations for criteria on medical examinations for driver limitation under certain specified conditions; Suggested that an appropriate committee of the AMA work with the United States Public Health Service and the industry in providing a type of detergent that will assure safety to the health of the public; Urged that the term "the aging" be used instead of "the aged" in all statements by the medical profession regarding older persons;

Approved the "Guides for Medical Society Committees on Aging" and recommended their wide distribution and use;

Received a progress report from the Commission on the Cost of Medical Care, which will present its final report in June, 1964;

Agreed that the Committee on Rehabilitation should be reconstituted and that it should include participation of knowledgeable representatives of all related fields of the practice of medicine;

Earnestly recommended that the state medical societies explore the advantages of implementing KERR-MILLS programs in a manner which will permit the care of beneficiaries under voluntary health insurance programs;

Resolved that the AMA attempt to have removed from the Kefauver-Harris Amendment those provisions which authorize the U.S. Food and Drug Administration to determine the effectiveness of drugs; Reaffirmed the Association's policy of opposing the inclusion of self-employed physicians under Social Security;

Agreed that a short form medical record may be used in cases of a minor nature and, in general, should apply to hospital stays of 48 hours or less;

Approved a Board of Trustees conclusion that the Honors and Scholarship Program, originally proposed in 1960, not be implemented in the light of present circumstances, and

Urged all AMA members to continue to support the Woman's Auxiliary so that it

Continued on Page 227

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Each teaspoon (5 ml.) contains codeine phosphate 5 mg.,
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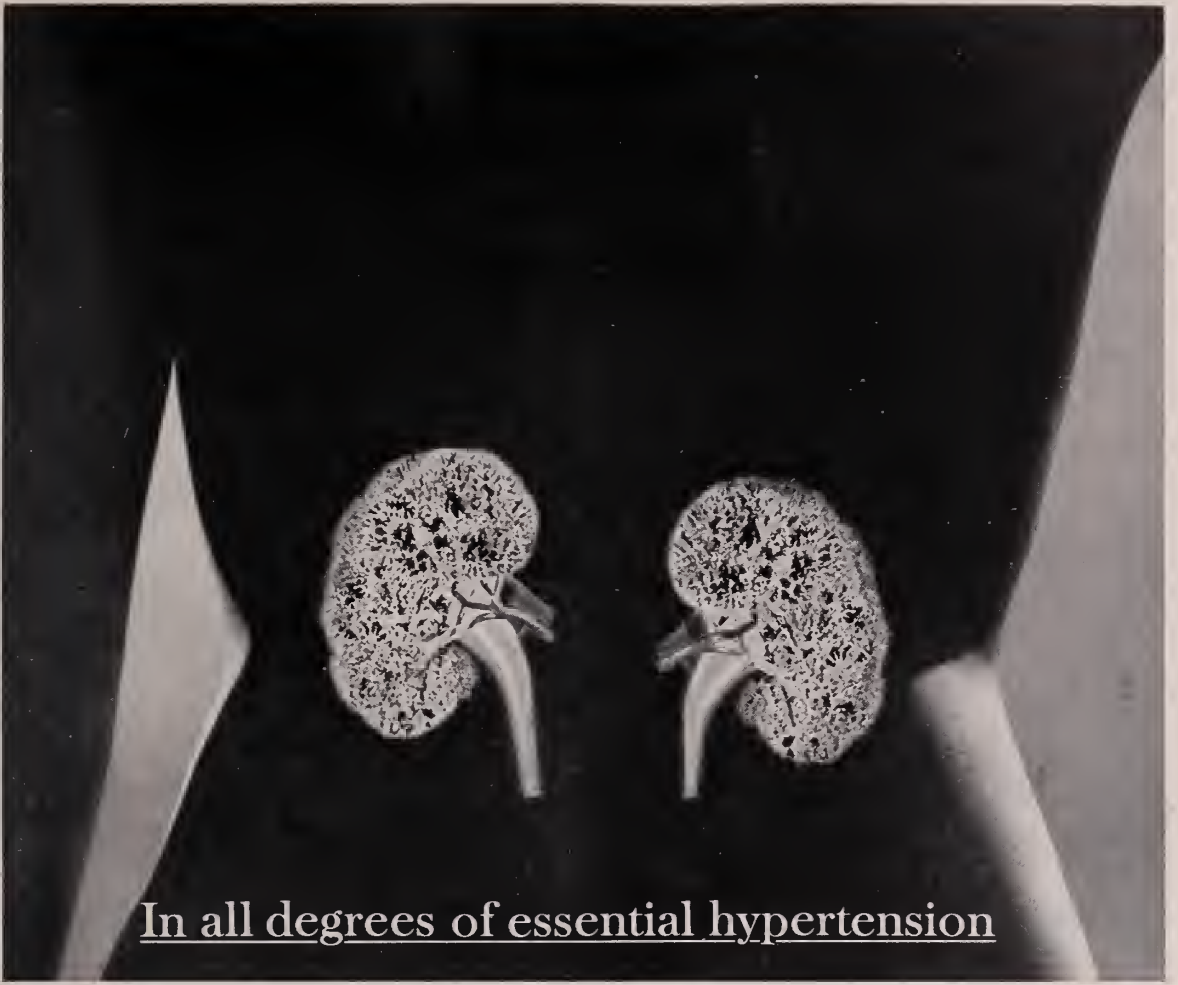
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References: (1) Moyer, J. H., and Heider, C.: Am. J. Cardiol. 9:920 (June) 1962. (2) Brest, A. N., and Moyer, J. H.: Pennsylvania M. J. *63*:545 (Apr.) 1960. (3) Berry, R. L., and Bray, H. P.: J. Am. Geriatrics Soc. *10*:516 (June) 1962. (4) Hutchison, J. C.: Current Therap. Res. *4*:610 (Dec.) 1962. (5) Feldman, L. H.: North Carolina M. J.: *23*:248 (June) 1962.

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Bibliographical references should be limited to twelve and should be typed in conformity to the method used by the Index Medicus. They should be numbered consecutively in the order in which they first appear in the text. Book references should give the name of the author, title, edition number, publisher, and the year.

Illustrations (photographs, tables, and graphs) should be submitted on separate sheets of paper and not combined in the text. Instructions for combining photographs are acceptable.

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*Donnelly, J.: A.M.A. Arch. Environmental Health 6:697, June, 1963

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President's Letter

At its December, 1963, meeting the Council of the Minnesota State Medical Association took an action which I consider to be particularly praiseworthy and significant. The action is concerned to quite an extent with finances. Appropriately, it was initiated by your treasurer, Karl Anderson, who deserves complimentary regard for his efforts in the matter.

For each of the past two years, an anonymous donor has contributed $1,000.00 to the Minnesota Medical Foundation to be used as a Distinguished Teaching Award. The donor and the Foundation realized the benefits that often accrue to those who are engaged in research projects. They felt that there should be a way to recognize and reward superior individual teaching achievements by a member of the University of Minnesota Medical School faculty, thus also honoring the profession of academic medicine. The Award was intended for the benefit of younger members of the full time faculty, specifically those holding the academic rank of instructor, assistant professor or associate professor.

The Minnesota Medical Foundation has been given notice that the Award will no longer be available from the original donor. This is where Dr. Anderson, your funds and your Council enter the picture.

It was brought out that the Association has an investment account, developed over the years, of an amount equal in value to our present annual budget. This seems to be a desirable goal among medical organizations. Although not always achieved by such groups the situation is not criticized by those who determine the tax status of the Association. Naturally the investment account earns income. This income has previously been entirely reinvested. It appears reasonable that part of this income should be used for the good of the medical profession now, rather than providing unnecessarily liberal amounts for an emergency which may never emerge.

Dr. Anderson has been closely associated with the Minnesota Medical Foundation and particularly interested in the Distinguished Teaching Award. He testified to the real popularity of the Awards by all who are aware of the project. He pointed out a way to substantially augment the numbers in this cognizant group by doing a great service to medical education in Minnesota and at the same time to improve our public relations. He suggested two Awards of $1,000.00 each to be presented to two faculty members for achievements in teaching rather than for distinction in laboratory research. One award would be given in clinical medicine and one in basic science. The Medical School Student Council, cooperating with the student body, would recommend recipients and the Minnesota Medical Foundation would make the final selection. The Awards would be presented by the President of the Minnesota State Medical Association at the Senior Recognition Day exercises which are held in the Mayo Auditorium.

Continued on Page 299

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Mammography for the Problem Breast*

DAVID M. WITTEN, M.D.**
Rochester, Minnesota

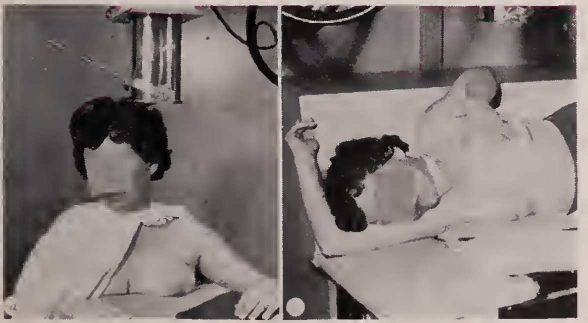

Fig. 1 — Positions for mammography: *(a)* cervicocaudad view and *(b)* oblique view.

THE RECENT development of an improved roentgenographic technic for examination of the breast has made available, on a practical basis, a valuable new diagnostic tool.

Roentgenography of the breast, or mammography as it is more popularly termed, was first attempted in the early 1930s; but, because of technical and interpretive difficulties, it failed to gain widespread acceptance. However, through the continuing interest of a few investigators, most prominent of whom were Leborgne[1] and Gershon-Cohen and Ingleby,[2] the basic principles of soft-tissue roentgenography as they apply to examination of the breast were defined and the roentgenographic characteristics of most benign and malignant lesions of the breast were described. Recently, Egan[3] has further refined soft-tissue roentgenographic technic; and, as a result of his outstanding success with mammography in the diagnosis of carcinoma of the breast, he has stimulated a widespread and growing interest in this examination.

Technic

Mammography is a soft-tissue roentgenographic technic in which no contrast medium is used. Based on the fact that roentgen rays generated at low voltage (20 to 35 kilovolt range) are absorbed more fully by skin, fibrous tissue, and tumorous tissue than they are by fatty tissue, the technic permits roentgenographic differentiation of these tissues. A special, slow, very fine grain, industrial type of roentgenographic film which is capable of depicting fine anatomic detail is commonly used for this examination.

Two views of the breast are ordinarily made. The first (Fig. 1a), the so-called cervicocaudad view, is made with the patient seated. The breast is supported on a film holder and the beam is directed through the body of the breast from above downward. The second (Fig. 1*b*), an oblique view, is made with the patient on her side. Again the breast is supported from below by the film holder, but in this view the beam is directed laterally through the body of the breast. These two views demonstrate the major portion of the breast and, since they are made at right angles to each other, permit accurate localization of any lesion in the breast. In problem cases, a third projection through the axilla is sometimes made for study of the axillary tail of the breast and to demonstrate enlarged axillary lymph nodes.

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*Read at Minnesota State Medical Assn. Meeting, Duluth, Minnesota, May 20-22, 1963.

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Diagnosis

The primary objective of mammography is to differentiate between malignant and nonmalignant lesions in the patient with palpable breast disease and to detect carcinoma of the breast when its presence is not suspected from the history or the physical examination.

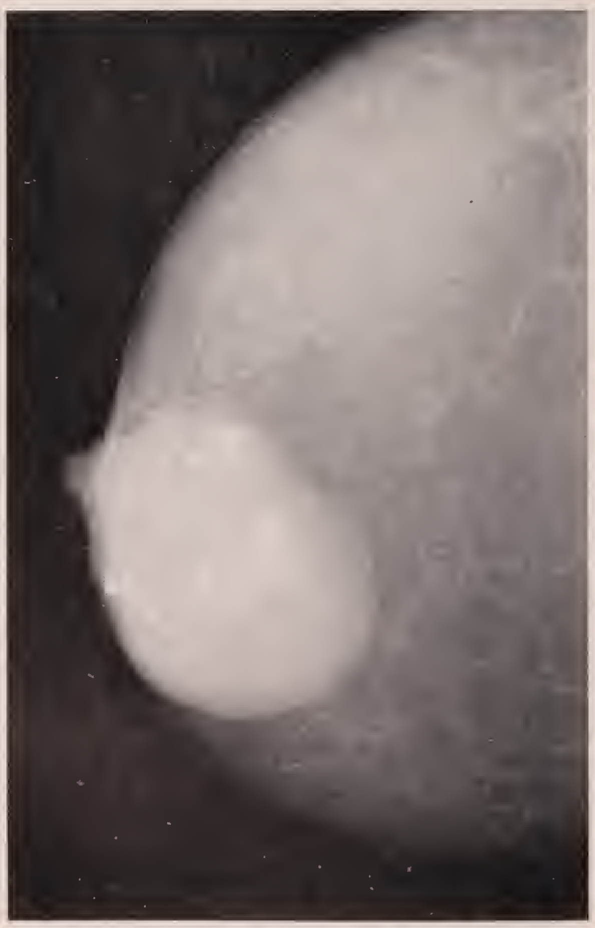

Fig. 2 — Typical benign lesion of breast (fibroadenoma). Margins are circumscribed and mass is homogeneously dense. Coarse calcification is present within the tumor in this case.

The differentiation of a malignant from a nonmalignant lesion and the detection of occult carcinoma require not only films of the highest quality but also interpretation by a roentgenologist who has a thorough knowledge of both the pathologic anatomy of the breast and the various roentgenographic appearances of the normal and the diseased breast. Mammography is *not* an examination which should be attempted by any physician who does not have available equipment modified for low kilovoltage work or who is untrained in the conduct and the interpretation of the examination.

The roentgenographic features of both benign and malignant lesions of the breast are in general relatively specific, although none is pathognomonic. In our experience, the majority of such lesions can be identified and differentiated without undue difficulty, but atypical lesions are common and roentgenographically dense breasts found in some patients defy satisfactory roentgenographic examination.

The classic benign lesion (Fig. 2) is well circumscribed and of homogenous density throughout. Benign lesions are characteristically surrounded by a thin halo of radiolucent fat and tend to be multiple. Occasional lesions, such as the fibroadenoma illustrated in Figure 2, contain coarse deposits of calcium. In general, the well-defined margin of the benign tumor clearly differentiates it from carcinoma.

Malignant lesions can assume a variety of roentgenographic patterns, but commonly there is a mass with an irregular margin produced by invasion of surrounding tissues. The classic example of a malignant lesion is the spiculated mass formed by scirrhous adenocarcinoma (Fig. 3). The mass is dense in the center and fades out towards the periphery. The margin is irregular, and spicules of tumor extend outward for various distances into the surrounding tissues. In advanced cases, localized thickening of the skin is present over the mass, and nipple retraction may be evident. In about one third of the cases of carcinoma, punctate calcification is visible within the tumor. The identification of this peculiar calcification is a valuable aid to diagnosis and, while not pathognomonic of the disease, strongly suggests carcinoma. Occasionally, calcification of this type is the only roentgenographic evidence suggesting the presence of a malignant lesion.

Indications

The principal indications which have been developed for mammography are:

A Palpable Dominant Mass in the Breast

Superficially, roentgenographic study of a dominant solitary mass in the breast seems unnecessary since prompt biopsy and histologic examination is indicated. Nevertheless, mammography is of value in these cases. It can provide information on the nature and extent of the disease process, which will aid in planning the operation; it may help avoid delay in treatment of carcinoma, which results from the common practice of waiting a month or two to see if a palpable nodule decreases in size; it can help remove uncertainty as to the actual presence of a mass; and, finally, it can reveal the presence of associated, yet clinically unsuspected, carcinoma in the same or opposite breast (Fig. 4).

Carcinoma of One Breast

Both preoperatively and postoperatively, carcinoma of one breast is a prime indication for mammography, as this technic can reveal carcinoma of the opposite breast at an early stage. Simultaneous bilateral carcinoma of the breast occurs in a small but significant number of patients. Frequently, one lesion is recognized clinically, but the second goes undetected unless identified roentgenographically (Fig. 5). Furthermore, after mastectomy for carcinoma, development of metastatic carcinoma or of a new primary lesion in the unoperated breast is a frequent occurrence. In these patients, mammography permits earlier diagnosis and presumably, therefore, more effective treatment.

Fibrocystic Disease

Patients with long-standing fibrocystic disease and recurrent cyst formation are clinical enigmas. In many of these patients, the breasts are filled with palpable nodules making identification of small underlying carcinomas difficult; in others, diagnosis of carcinoma is delayed because both the surgeons and the patients are reluctant to plan further operations when repeated biopsies have

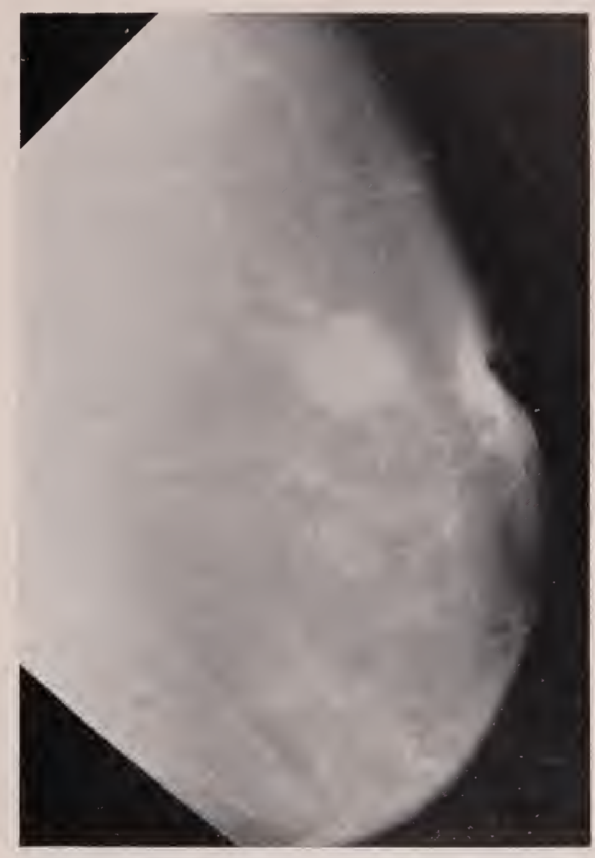

Fig. 3 — Typical malignant lesion of breast (scirrhous adenocarcinoma). Margins of mass are irregular and spiculated. Associated nipple retraction, skin thickening, and increased vascularity are present. Fine, stippled calcification is seen in other cases.

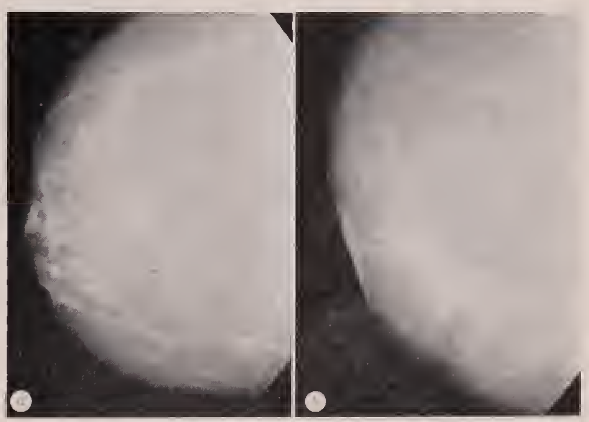

Fig. 4 — *(a)* Palpable benign lesion of right breast. *(b)* Clinically unsuspected carcinoma of left breast.

revealed nothing but cysts. As a result, these patients have proved to be our most fertile source for clinically unsuspected carcinoma.

Discharge From Nipple, Whether Serous or Sanguinous

In patients complaining of nipple discharge, nonpalpable carcinoma may be detected by mammography and benign lesions frequently may be identified and localized. A lesion can usually be demonstrated when present; and, if no evidence of carcinoma is seen on the roentgenogram, mammography gives added assurance to the clinician planning conservative management of these problems.

Pain in the Breast

Localized breast pain is occasionally the only clinical evidence suggesting disease of the breast. In some patients with such pain, a small nonpalpable carcinoma can be demonstrated on the roentgenogram.

Metastatic Adenocarcinoma From Unknown Primary Lesion

Mammography has been of considerable aid in the study of patients with metastatic adenocarcinoma originating from an unknown primary lesion. Examination of the breast in the search for an occult carcinoma of the breast in these patients is simple and frequently rewarding. If carcinoma of the breast is identified, the management of the patient may be materially altered and the chance for better palliation improved.

Large or Diffusely Nodular Breasts

Mammography is of considerable value as a diagnostic aid for evaluation of the large, diffusely lumpy breast. Breasts of this type present difficult problems in physical diagnosis; yet they lend themselves well to mammography because of their large fat content. In these breasts, carcinoma is ordinarily easily identified and accurate roentgenographic diagnosis is possible.

Accuracy

The value of mammography depends on its reliability as a method for detection and differentiation of various diseases of the breast. In the hands of an experienced interpreter, the large majority of malignant breast tumors can be identified and correctly diagnosed preoperatively.[7] The accuracy of this examination in our hands is indicated in Table 1.

Of approximately 5000 patients comprising our initial group studied by this technic, 622 have had histologic proof of diagnosis. Benign lesions were found in 394 cases and carcinoma in 228. A preoperative diagnosis

TABLE 1
Diagnostic Accuracy

Pathologic Diagnosis	Cases	Roentgenographic Diagnosis Correct	Roentgenographic Diagnosis Incorrect	Accuracy, Percent
Benign	394	345	49	88
Malignant	228	193	35	85
Total	622	538	84	86

TABLE 2
Clinically Unsuspected Breast Cancer
Diagnosed by Mammography

Indication for Mammography	Cases
Fibrocystic disease; no suspicious mass	7
Previous mastectomy for carcinoma	5
Nodular breasts; no suspicious mass	5
Nodule in opposite breast	4
Routine examination	3
Metastatic adenocarcinoma; primary unkown	2
Nipple discharge	1
Total	27

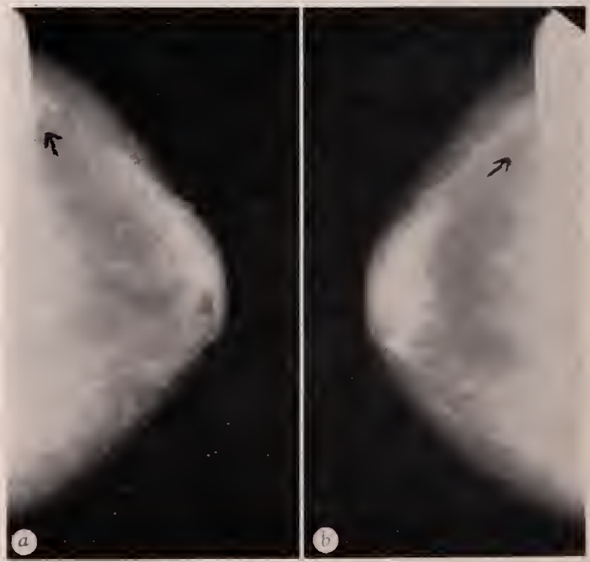

Fig. 5 — Bilateral clinically unsuspected carcinoma in a patient with longstanding fibrocystic disease.

of benign or probably benign lesion was made from the mammograms of 345 of the 394 patients with benign lesions, an accuracy of 88 per cent; a preoperative mammographic diagnosis of malignant or probably malignant lesion was made in 193 (85 per cent) of the 228 cases of carcinoma of the breast.

Both false negative and false positive mammographic diagnoses occur. A false positive diagnosis of carcinoma is apt to be made in those cases where the lesion mimics carcinoma in its gross form. Breast abscess is the worst offender in this regard; but other lesions, infected cyst, sclerosing adenosis, and plasma cell mastitis, to name but a few, can occasionally produce a roentgenographic appearance which cannot be differentiated from carcinoma. Palpable carcinoma, on the other hand, may be difficult or impossible to diagnose in some cases. A false negative diagnosis is made most frequently when carcinoma is obscured by overlying dense parenchymal tissue, but the diagnosis can sometimes be missed when the lesion is not projected onto the film because of its location at the extreme periphery of the breast.

The figure of 85 per cent does not entirely reflect the value of mammography in diagnosis of carcinoma; for, while most of the lesions were palpable and warranted biopsy on clinical grounds, 27 (12 per cent) of the 228 carcinomas in this series would not have come to operation were it not for the diagnosis of carcinoma by mammography (Table 2). Fifteen of these malignant lesions were truly occult, as they could not be identified by palpation even in retrospect after identification and localization on the mammogram. The other 12 carcinomas could be identified in retrospect after the mammographic diagnosis of carcinoma as palpable areas of nodularity in the breast. However, in no case had the clinician suspected the presence of carcinoma on the basis of the initial physical examination and none of the 12 would have come to operation without the mammographic diagnosis of carcinoma.

Comment

Mammography is a useful diagnostic examination which can aid the clinician in evaluation and management of patients with disease of the breast. Successful application of this technic in clinical practice requires, however, that the limitations as well as the virtues of the method be clearly recognized and their importance fully understood by both the roentgenologist interpreting the films and the clinician seeking roentgenographic assistance.

Mammography is *not* an infallible diagnostic tool which can replace either the physical examination for detection of breast disease or biopsy and histologic examination of tissue for definitive diagnosis. As has been pointed out, some palpable carcinomas are obscured by dense breast parenchyma while others mimic benign processes in roentgenographic appearance; for this reason, a clinically suspicious mass in the breast must be biopsied regardless of the mammographic diagnosis. Furthermore, since benign lesions can occasionally produce a roentgenographic appearance which mimics that of carcinoma, a radical mastectomy should never be performed on the basis of a mammographic diagnosis of carcinoma without prior histologic proof of malignancy.

In spite of these deficiencies, mammography is clearly an effective supplement to the history and the physical examination. Preoperatively, it can help define the nature and extent of a palpable lesion and aid in operative planning; in other cases, it can demonstrate the presence of significant disease, especially carcinoma, when it is not suspected on the basis of the history or the physical examination; and, finally, mammography is a diagnostic tool which can give added assurance to both physician and patient in the conservative management of many common breast complaints.

Summary

The development of mammography is a useful advance in diagnostic technic for study of the breast. When used as an adjunct to traditional methods for evaluation of disease of the breast, it is possible to improve diagnostic accuracy and, in a significant number of cases, to detect the presence of carcinoma when it is not suspected on the basis of the physical examination alone.

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WHAT'S YOUR DIAGNOSIS?

Three years ago, at the age of 24, this man presented himself for examination because of pain in the right side of the abdomen associated with tenderness in the right renal area. Intravenous pyelogram showed a questionable deformity at the lower pole of the right kidney, but the consulting urologist felt that the urinary tract was normal. The physical examination was otherwise noncontributory, and cholecystogram and X ray of upper gastrointestinal and colon revealed no abnormality.

Six months ago this man was again studied because of pain in the left side of the abdomen associated with tenderness over the left renal and splenic area. A questionable mass in the left upper quadrant disappeared after a few days of observation. Moderate pyuria was noted, but intravenous pyelogram again showed prompt bilateral function and the urologist found no significant abnormalities but made a diagnosis of left pyelonephritis without obstruction. The symptoms subsided.

Past history was negative except that his appendix had been removed at age eleven and an inguinal hernia had been repaired at age five.

Three weeks ago he was again examined because of acute epigastric and right upper quadrant pain. There was no jaundice and the tenderness subsided rather promptly. An X-ray examination revealed stones in the gallbladder. Chest X ray was negative. Urine was negative and the blood counts were normal. X ray of the skull revealed calcification within the cranium. There was a small skin lesion on the face. He had a butterfly-shaped rash on his nose and cheeks and his IQ seemed a bit subnormal.

Because of the finding of stones in the gallbladder a cholecystectomy was done. During exploration an irregular mass was found involving the right kidney and a similar nodularity was found in the left kidney, though not so evident. A biopsy was taken from this nodular mass in the region of the right kidney.

What's Your Diagnosis? Turn to page 257.

BALLANCE'S SIGN

Ballance's sign is evidenced by dullness in both flanks, but the dullness on the right side shifts when posture is changed. The dullness on the left persists. This is said to be pathognomonic of splenic rupture. There is blood in the peritoneal cavity, but the blood in the neighborhood of the lacerated spleen has coagulated, thereby accounting for the absence of shifting dullness.

Past experience should be a guide post, not a hitching post.—D. W. Williams

Electrofulguration

New Surgical Method for Varicose Veins

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THE STRIPPING operation is the prevailing method of treating varicose veins. This has been the most successful operation to date, but both doctors and patients have not been completely satisfied. The patient is sometimes left with multiple disfiguring scars. In addition, persistence and recurrence of varicose veins are so common that the patient is often warned of this prior to surgery. For the conscientious surgeon the operation can be long and tedious.

We are reporting a new method of treating varicose veins. The longest period of follow-up on a patient has been one year and, at this time, a preliminary report is being made.

In the conventional varicose vein-stripping operation the greater and short saphenous veins are usually straight tubes and can be easily removed using intraluminal strippers. However, the tortuous veins, the large venous plexuses, the veins in the anterior, lateral, and posterior thigh and calf do not permit passage of strippers. These veins must be removed by dissection through multiple incisions. This is tedious surgery and is often omitted or done inadequately. If the surgery is done thoroughly, the patient may be left with many incisional scars. If these veins are left, the patient commonly has a persistence of varicose veins.

In our method these veins are destroyed with electrofulguration rather than removed. With the assistance of the engineers at the Medtronic Company a special electrode was designed for this purpose.

The Instrument

The instrument consists of three components: (1) a fulguration generator, (2) a timer, (3) the electrode. The fulguration generator provides the high frequency fulguration current. The timer controls the length of the discharge. The electrode is a one-eighth-inch diameter steel shaft with a handle on one end. On the opposite end is a pointed steel tip from which the arc discharge arises.

Technique

The patient is admitted to the hospital on the day prior to surgery. On this day his legs are marked very carefully with indelible ink. He must be standing on a stool, and good lighting is imperative. Every varicose vein on the leg must be carefully mapped out with the ink. Small early varicose veins are also marked. Large venous plexuses are carefully outlined. Perforators are identified.

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The Saphenous Vein

At surgery a careful saphenous ligation is done. The long saphenous vein is picked up at the ankle or foot through a small incision and stripped to the inguinal incision. This can usually be done with one stripper. Sometimes an additional incision is necessary at the medial knee or calf.

The Tortuous Radicals

The remainder of the operation is done with the electrode, which is inserted under the skin through a small stab incision made with a number fifteen Bard Parker blade. The electrode is advanced under the skin adjacent to the skin marks; it is not passed down the lumen of the vein. Using the skin markings, the electrode is placed as close as possible to the vein; this may be under, over, alongside, or transversely through the vein. When the tip is in the desired position, the button switch on the handle is touched and a half-second arc discharge occurs. The tip of the electrode is then advanced or withdrawn a short distance and the switch again pressed. In this way all areas of tortuous veins are quickly destroyed. The shaft of the electrode is nine inches long and can be passed long distances under the skin to destroy the veins.

During this fulguration period the patient is kept in slight trendelenberg to empty the veins of blood. The purpose of timing the discharge to one-half second is to avoid the possibility of skin burns. Perforators are likewise destroyed in the same manner. However, the electrode tip is pointed down near the fascia and a longer discharge given. If the patient has incompetent, short, saphenous veins, these are stripped in the conventional manner.

Using this technique, stripping the most extensive tortuous varicose veins takes very little longer than stripping the long saphenous veins.

Wrapping the Leg

Upon the completion of surgery the legs are wrapped with a layer of kurlex and then bound tightly with elastoplast from the upper thigh to the base of the toes. The foot of the bed is elevated and the patient is encouraged to walk the evening of the day of surgery.

Postoperatively the only pain is in the inguinal incisions. Patients describe a numbness in the calves and feet which sometimes lasts four to six weeks; they are surprised and elated, however, at the lack of pain and discomfort.

Results

The longest period of follow-up has been one year. In the initial operations only one vein or small areas on each patient were treated by fulguration. As the results were observed, fulguration was used more extensively until the present technique was evolved. It has now been used in forty patients. The operation accomplishes its purpose: it cures the varicose veins with a minimum of incisions and a good cosmetic result is obtained.

Possible Complications and Sequellae

There were some problems with the early models of the electrode. With improved design and construction, however, the instrument has been very successful.

One problem was skin burns. The timer was inserted in the circuit to prevent burning. However, care must still be used on the foot, on the anterior tibial area, and behind the knee, as these areas are the most vulnerable to burns.

Another problem is numbness. Apparently some of the superficial sensory nerves are temporarily injured or destroyed, resulting in a feeling of numbness in the calf and foot. Although this always disappears after a few weeks, some patients are annoyed by it.

Summary

A new method of treating varicose veins is proposed. Forty patients have been operated by this method and followed from one month to one year. We feel the operation and results are superior to those obtained with the conventional stripping and dissection technique. In our method the tortuous veins are destroyed by electrofulguration. The operation accomplishes its purpose of obliterating the varicose veins. The patient has a short, relatively painless postoperative course; and because of the few incisions the cosmetic result is superior to the prevailing method.

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Galen's Materia Medica*

Antidote for Snake Bite and Dog Bite

The flesh of vipers was an important ingredient in the famous antidote and remedy called "theriac,"** concerning which Galen wrote two special treatises besides discussing it in his works on simples and antidotes. He explains more than once how to prepare the viper's flesh, why the head and tail must be cut off, how it is cleansed and boiled until the flesh falls from the backbone, how it is mixed with pounded bread into pills, how the flesh of the viper is best in early summer. He is skeptical as to whether or not the liver of a mad dog will cure its bite, indicating with a deliciously sly inuendo that many say so, and he knows of some who have tried it and survived, but they took other remedies too.

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*Thorndike, Lynn — see Minn Med Oct. '63.
**An antidote for snake bite.

ANSWER TO WHAT'S YOUR DIAGNOSIS

(From page 254)

Fast frozen sections of the biopsy revealed a nonmalignant process. The subsequent paraffin sections were reported to show an angiomyolipoma characteristic of tuberous sclerosis. A subsequent biopsy of the skin lesion on the face confirmed the diagnosis and the skull X rays revealed calcification characteristic of this disease.

See Bourneville's Syndrome Page 271.

Over-sleeping and over-eating hurt more people than over-working.
—Forbes Epigrams

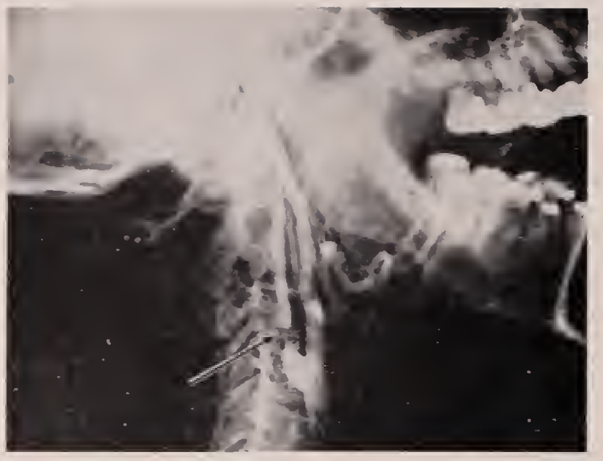

Fig. 1. Left — Cervical carotid angiogram demonstrating partial stenosis of right internal carotid artery.

Extracranial Vascular Occlusive Disease*

THE RECOGNITION of segmental occlusive disease in the extracranial portion of the vascular tree as a cause of cerebrovascular insufficiency has been publicized with increasing frequency in recent years.

At the same time the acceleration of progress in vascular surgery has made it inevitable that the two should meet. This union of vascular surgery with the problem of the stroke has become a major subject in surgical literature. First reports described a new, spectacular and bold attack on arteries, not previously allowed, followed by numerous reports from several centers containing series of cases of cerebrovascular surgery with associated results, morbidity, and mortality.[2-9] More recent reports have been concerned with improvement in selection of candidates and technical refinements of the operative procedure itself.[10,11]

This present report reflects this trend and advance. Because of some remarkably encouraging successes as well as some most disconcerting failures, we were stimulated to review our cases in hope of disclosing any factors which would improve the results.

Clinical Aspects

At the time of this report eighty-four patients have been seen with symptoms and signs of cerebrovascular problems. Fifty of these patients have come to surgery in an attempt to relieve cerebrovascular insufficiency, and this report is primarily concerned with this group. Another twenty-five patients have undergone angiography without showing evidence of occlusion outside of the skull, and an additional nine patients have been seen because of prominent pulsatile vessels in the neck or tumors involving the carotid arteries.

The mean age of the fifty patients coming to surgery was sixty-one years with a range

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*Presented at the Minnesota Surgical Society Meeting, Duluth, Minnesota, July 12, 1963.

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An Analysis of Fifty Cases Treated Surgically

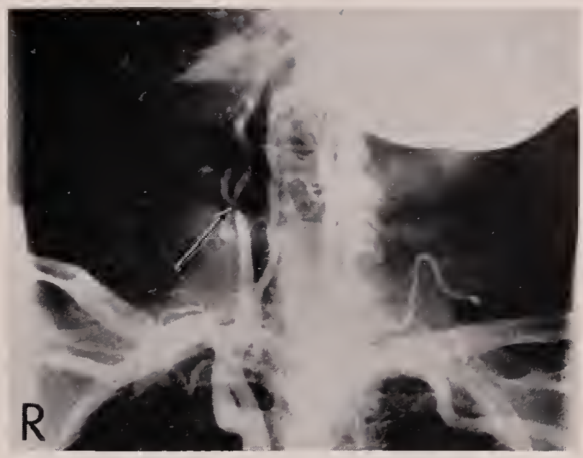

Fig. 1. Right — Retrograde angiogram from aortic arch showing both carotid and both vertebral vessels with severe stenosis of right internal carotid artery.

of forty-five to eighty-one years, with a moderate preponderance of male patients (32 M : 18 F). Presenting symptoms ranged from a singular "buzz" in the neck without neurological symptoms to complete unconsciousness and hemiplegia following a major cerebral infarction. Table 1 contains an attempt at clinical division and classification. A clear-cut identification of any patient with one of the classes is not always possible because of blending of one class with another. For example, it may not be possible to separate Class III, the so-called progressive cerebral infarction, from Class IV-A, the completed acute stroke. Nevertheless, we think it important to attempt such a division at the present time.

It is noted that slightly more than one half of the patients in the present series fell into the transient-episode group. The most common symptom was dizziness. Syncope and numbness or clumsiness of an extremity and headache followed closely. Difficulty with vision was frequently present but was not often a presenting complaint or initially recognized as a signal of vascular insufficiency. Confusion was more commonly associated with the transient stroke. Headache, tinnitus, vertigo, and ataxia were associated with the vertebral-basilar artery type of insufficiency. The most common sign was the presence of a cervical bruit. Decreased carotid pulsations were not frequent and were not considered reliable.

Laboratory Aspects

The keynote of diagnostic procedures is the angiogram to determine the position, type, and degree of obstruction. (Fig. 1)

The best angiographic study is the one which yields the most complete information. A retrograde arterial study with injection from the aortic arch will include visualization of all four vessels in the neck as well as the cerebral arterial tree. Clear angiographic detail of the cerebral vessels may be sacrificed somewhat by this method, and for this reason we have occasionally followed such a retrograde study with a percutaneous puncture of the cervical carotid if we felt that completion of the study was mandatory.

Several patients in this report have come to surgery with a unilateral or bilateral carotid puncture study only, and in four patients the urgency of the problem brought them to surgery without angiography. However, we feel that a future review of results will be better clarified if the angiographic study is complete and includes all of the cervical as well as the cerebral vessels.

Complications

Table 2 lists the type of angiographic study of the patients in this report together with the number of complications encountered in each type. It should be noted that the bilateral carotid puncture technique was associated with a high incidence of complication. Without more thorough analysis of the details of technique and the state of the patient at the time of examination, such an incidence is probably not statistically significant. Nevertheless, each of the five patients suffered some progression of hemiparesis, speeding the need for surgery. This is in contrast to the relatively low incidence of complications after unilateral puncture, namely one transient right hemiparesis after angiogram. With retrograde angiography one patient suffered a progression of hemiplegia and one a transient stroke lasting twelve hours with complete recovery; another patient complained of numbness along the sensory distribution of the median nerve following a percutaneous axillary artery catheterization. The three complications in the combined retrograde and cervical puncture studies were a hematoma in the groin (not requiring evacuation) following a femoral puncture, and a double complication of a loss of radial pulse, the patient complaining of a cold hand following brachial artery cutdown, as well as an infection at the cutdown site.

In addition to angiography, lumbar puncture with examination of the spinal fluid and electroencephalographic study have been useful mostly in separating other disease entities. Ophthalmodynamometry only supported the clinical impression of deficient unilateral blood flow.

Technical Aspects

Fifty patients underwent surgery, three for vertebral artery repair and forty-seven for carotid surgery. Seven had bilateral carotid surgery.

Anesthesia was general endotracheal for the most part (thirty-seven cases). We feel this offers the best opportunity for the highest cerebral oxygenation and blood flow.

Anticoagulant

Anticoagulant in the form of Heparin is used during the operative procedure by direct injection into the internal jugular vein and is frequently antagonized with an equal amount of Protamine following removal of the shunt and closure of the arteriotomy. We have not advocated the use of anticoagulants postoperatively in patients who have had successful repairs.

TABLE I
Extracranial Vascular Occlusion
Clinical Classification

	Clinical Complex	Duration	Number of Patients
Class I	Symptoms Only	Momentary to Persistent	17
Class II	Transient Stroke (With Complete Recovery)	Less Than 1 Hour	11
Class III	Progressive Cerebral Infarction (Advancing Stroke, "Stroke in Evolution")	Hour by Hour	6
Class IV-A	Completed Stroke—Acute	Less Than 1 Week	9
Class IV-C	Completed Stroke—Chronic	More Than 1 Week	7

Cerebral Blood Flow

Cerebral blood flow during endarterectomy was maintained by use of an internal shunt in all cases of partial occlusion, with only two exceptions, one of which met with serious technical difficulty. In cases of complete obstruction the shunt was not used if retrograde flow could not be demonstrated after removing the block. A size 10 Bardic Catheter (Fig. 2) is firm enough to allow control in positioning and soft enough to allow easy removal, and therefore at present our choice of shunt.

Surgical Technique

The surgical technique itself is not prolonged or involved. For the carotid vessel, the artery is exposed and, with a minimum of manipulation, encircled with umbilical tape above and below the bifurcation. At this point in ten of our patients, pressure measurements above and below the obstruction were taken by insertion of a thin-walled size 18 needle attached by PE Tubing to a strain gauge transducer and channel recorder, or simply to a Tycos anaeroid manometer. Following this, vascular clamps are placed across the external, internal, and common carotid arteries and a longitudinal incision is made, beginning on the internal carotid artery, distal enough to get beyond the highest point of disease. This permits introduction of the internal shunt with ease and without danger of advancing emboli into the cerebral circulation, and also allows adequate visualization of the intima at the distal site of endarterectomy in the internal carotid artery. The endarterectomy itself is performed easily by careful sharp and blunt dissection. Following removal of the plaque (Fig. 3), the vessel is usually wide enough to allow primary closure without a patch graft. Occasionally taching sutures on the shelving intima are necessary. In those cases where the disease process is a result of an extensive arteriosclerotic plaque without recent clot or ulceration, a patch graft of woven teflon is sutured to the edges of the arteriotomy without attempting to remove the plaque. Before the final two or three sutures are placed, the shunt is removed and the vessel occluded momentarily as the arteriotomy closure is completed. In this series the surgical technique consisted in endarterectomy alone in twenty-six cases, endarterectomy and patch graft in thirteen, and patch graft only in five, without endarterectomy. Eleven patients had other procedures, viz., dissection and exploration — five, thrombectomy — four, interposition tubular graft — one, and ligation of a vessel (aneurysm) — one.

TABLE 2
Angiography — Extracranial Vascular Occlusion

	Cases	Complications
1. Cervical Carotid Puncture.		
Bilateral	10	5
Unilateral	16	1
2. Retrograde Via Catheter from Femoral, Brachial, Axillary, and Subclavian.	13	3
3. Combined 1. and 2.	7	3
4. Not Performed.	4	
	—	—
	50	12 (24%)

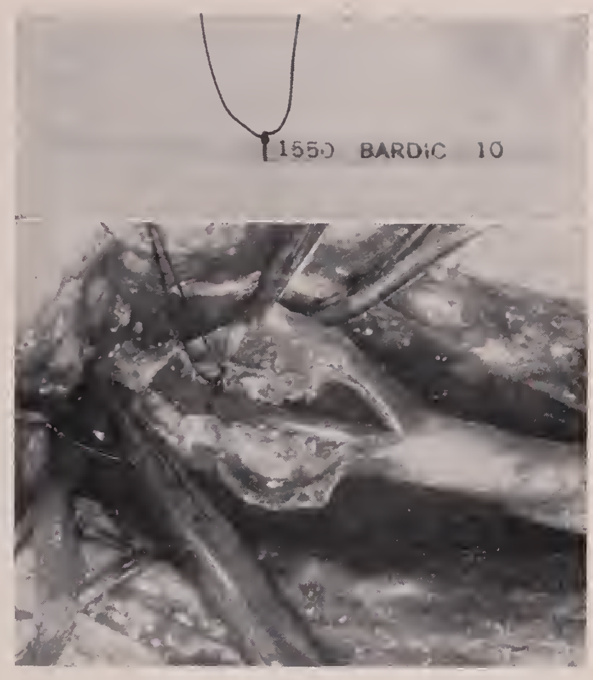

Fig. 2 — Internal Shunt. Above: Bardic #10 Catheter with #00 silk suture. Below: Shunt in place in carotid artery bifurcation prior to endarterectomy.

Operative Findings

Table 3 contains a list of the operative findings. These followed the angiographic interpretations without exception. It is interesting to note that in the fourteen cases of

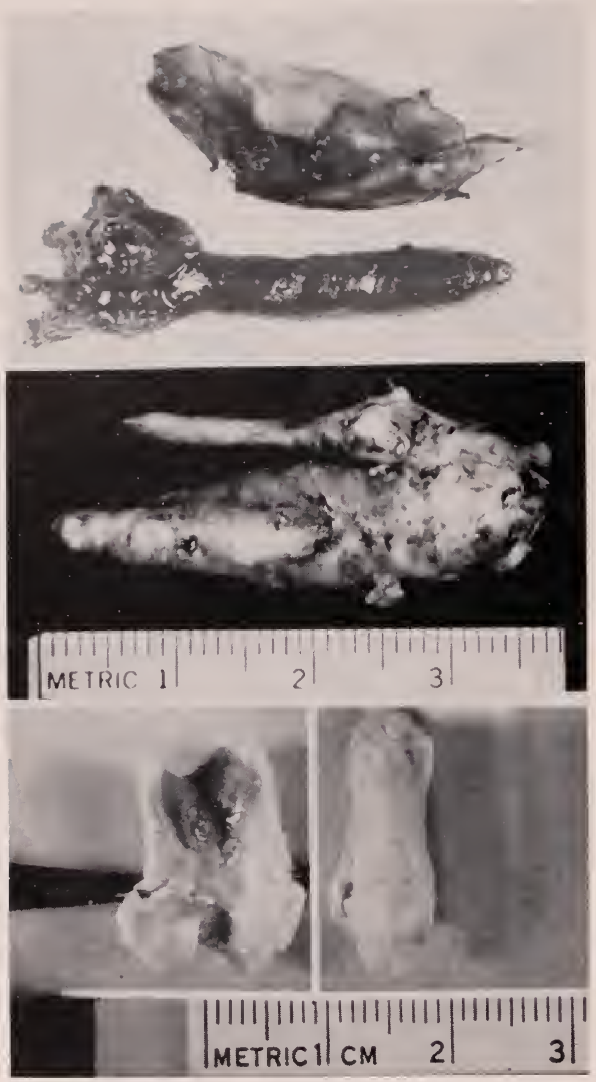

Fig. 3 — Typical thrombus and arteriosclerotic plaques removed from patients in this series.

complete block, four had partial obstruction on the opposite side and underwent bilateral surgery. In none of these four was flow re-established on the completely obstructed side. Of the ten remaining patients with a complete obstruction, five had restoration of carotid circulation with excellent back-flow after removal of the clot and plaque. Two of these patients died postoperatively from clinical progression of infarction. However, one of these patients, with flow re-established after complete occlusion, had an excellent result, and two had good results even though the period of occlusion in one was clinically nine days old.

TABLE 3
Extracranial Vascular Occlusion
Operative Findings

Number	Occlusion		Back Flow		Fibrin	
Carotid Vessels 54	Complete	14	No:	9	No:	16
	Partial	36	Yes:	45	Yes:	28
	None	4			Not Recorded	10
Vertebral Vessels 3	Complete	0				
	Partial	3	Yes:	3	None	

Results

Complications — Table 4

Injury to the hypoglossal nerve with temporary tongue hemiparesis was the most common complication and recorded in three patients, all in the acute completed stroke group. One of these patients underwent staged bilateral carotid surgery with a three-day interval to allow tongue adjustment following some mild difficulty after the initial surgery. Upon endotracheal extubation following the second operation he had high ventilatory obstruction due to relaxation of his tongue and pharynx and required a temporary tracheostomy for four days.

Deaths

All of the deaths occurred in the progressive infarction or completed stroke groups. All were neurological deaths due to cerebral infarction and occurred in spite of or possibly associated with surgery, although in only one case are we aware of any technical complication.

A summary of the postoperative deaths is as follows:

1. R. L., 47, male, acute stroke twenty-four hours duration. Angiogram showed a complete obstruction of the left internal carotid. A large arteriosclerotic plaque was removed. Good flow was restored. Inter-

TABLE 4
Extracranial Vascular Occlusion
Deaths and Complications

Deaths		Complications
Class I	0	3 — Hemorrhage Hematoma Horner's Syndrome
Class II	0	2 — Numbness Along Jaw Hoarseness
Class III	2	0
Class IV-A	2	3 — Hypoglossal Nerve Paresis
Class IV-C	1	0
	—	—
Total:	5 (10%)	8 (16%)

nal shunt not used. Anesthesia: general. The patient remained comatose and died forty hours after surgery.

2. S. B., 50, female, progressive symptoms and signs of carotid insufficiency and cerebral infarction for six days. Endarterectomy and patch graft performed for complete occlusion of right internal carotid artery. Good flow established, internal shunt used. Anesthesia: local. No difficulties during surgery. Postoperatively her symptoms of progression continued with a massive seizure eighteen hours postop. Re-explored to rule out thrombosis of graft. None was found. Developed respiratory arrest and placed on ventilator. Died two days later. Autopsy not permitted.

3. J. H., 70, female, signs and symptoms of stroke. Angiogram done on third day. Surgery on fifth day. The entire common carotid clotted. Thrombectomy and endarterectomy performed without restoration of flow. Died on sixth day.

4. C. L., 70, male, bilateral disease. Left side endarterectomy and patch graft. Local anesthesia. No internal shunt. No difficulty. Two weeks later right side was operated upon. Local anethesia. No shunt. Developed stroke during endarterectomy. Died two days later.

5. A. M., 81, female, right stroke, transient, one week prior to admission. Right stroke and aphasia soon after admission. Angiogram — combined study, showed severe stenosis left internal carotid artery and absent left anterior cerebral artery. Progressive signs and symptoms after angiogram. Endarterectomy. General anesthesia. Internal shunt used. Postop showed progressive deterioration. Died sixty hours later.

Neurological Results

In a disease of such mobile and labile manifestations as cerebrovascular insufficiency, the surgeon evaluates his results with a certain caution and an awareness that the dynamic factors of pathogenesis and repair taking place at the time of operation and postoperatively may cloud the exact nature of the surgical effect on the disease process.[12,13] Furthermore, the significance of surgical treatment cannot be fully evaluated or appreciated until long term results of treatment are available in five to ten years.

Bearing this in mind, we have attempted to classify the results of operation in these fifty patients in the light of prevention of further cerebral infarction and clearing of symptoms according to the scheme listed in Table 5. It is noted that the best results have been in the transient stroke group (Class II) followed closely by the symptoms-only group (Class I). The two excellent results in the chronic completed stroke group (Class IV-C) included a forty-eight-year-old man with a nine-day-old hemiplegia, who had complete return following endarterectomy and restoration of flow, and a sixty-nine-year-old man with fluctuating weakness of his right arm and leg and a consistently positive Babinski sign on the right after a stroke three years before surgery which reversed after bilateral carotid surgery.

Summary

1. Fifty cases of patients undergoing extracranial vascular surgery for occlusive disease have been reviewed.

2. Angiography, preferably including a complete study of the carotid, vertebral and cerebral vessels, is the keynote of establishing a diagnosis of the surgically correctable lesion.

3. Occasionally, the urgency of the problem requires surgery on the basis of history and physical findings alone.

TABLE 5
Extracranial Vascular Occlusion

Results

Classification of Results
Excellent — Loss of symptoms. Complete clearing.
Good — Patient improved but persistent symptoms. Stroke Residual.
Poor — Further Symptoms. Progression of stroke.
Failure — Death from any cause.

	Excellent	Good	Poor	Failure (Death)
Class I	10	6	1	0
Class II	8	2	1	0
Class III	2	2	0	2
Class IV-A	2	4	1	2
Class IV-C	2	3	1	1
	—	—	—	—
Total:	24	17	4	5

4. The use of an internal shunt during endarterectomy is a safe and helpful adjunct to the surgical procedure.

5. The best results and lowest morbidity are found in those patients with symptoms alone or transient ischemic episodes.

6. Occasionally, good results can be obtained in the completed stroke patient with unilateral total occlusion of circulation, so that surgery should be considered when deciding his management.

7. Further careful follow-up studies are necessary to determine the long-range value of this surgery.

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IT'S THE LAW

If an employer secures the services of a physician to treat an ill or injured employee, the employer is not liable for injuries caused by the negligence of the physician. If the employer makes a profit from such transaction, however, he then becomes liable for the negligence of the physician employed by him. In that instance he is responsible for the competence of the physician he employs.

Work is something that when we have it we wish we didn't; when we don't have it we wish we did, and the object of most of it is to be able not to do any some day.
—Phoenix Flame

Acute Stroke

Biochemical and Therapeutic Studies

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Significant improvement in outlook for victims of cerebral vascular accidents has attended a more vigorous medical and surgical approach to the problem. This timely article apprises the clinician of recent advancements and the need for more detailed and searching evaluation of these patients.

BECAUSE OF an increasing incidence of cerebrovascular disease in our aging population, medical and surgical treatment of acute strokes has become a major public health problem. The purpose of this communication is to report recent progress in an investigative center devoted to the study of cerebrovascular disease.

Apoplectiform onset of neurological deficit may be produced by cerebral thrombosis, hemorrhage, or embolism; but it has now been shown by arteriographic and necropsy studies that the commonest cause of progressive stroke (or stroke in evolution) is thrombosis of a major cerebral vessel or its branches. Accurate diagnosis can usually be made by the astute clinician using the time-honored methods of assessing the medical history, together with the physical examination. Table 1 classifies common signs and symptoms according to the vascular distribution from which they derive. For simplicity, only the carotid and vertebral systems are considered.

Laboratory examinations should include study of the spinal fluid, electrocardiogram, electroencephalogram, evaluation of contributing factors such as diabetes, hypercholesterolemia, hypertension, anemia, polycythemia, arteritis, syphilis, gout, and adrenal cortical function.[1-3] Table 2 shows the commonly associated diseases with their incidence. To illustrate some of these considerations, the following case history is cited:

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*From the Departments of Neurology, Wayne State University, College of Medicine, Detroit Receiving Hospital and Harper Hospital, Detroit, and the Wayne Center for Cerebrovascular Research. This work was supported by grants from the U. S. Public Health Service and the Receiving Hospital Research Corporation. Associates Dr. Raymond B. Bauer and Dr. John Gilroy performed all the arteriograms discussed here and collaborated with me in the arteriographic studies; Dr. Fumio Gotoh collaborated in the biochemical studies, and Doctors M. Barnhart and J. F. Johnson participated in the studies of coagulation. Presented at the 112th Annual Meeting of the American Medical Association, Atlantic City, June 19, 1963.

TABLE 1

Unilateral Temporal (C) or Suboccipital Headache (V-B)	
"Light-headedness"	(C or V-B)
Vertigo	(V-B)
Blurring of vision	(V-B)
Mononocular blindness	(C)
Transient paresthesias unilateral	(C) bilateral (V-B)
Transient hemiparesis	(C) or quadriparesis (V-B)
Transient ataxia	(V-B)
Dysphasia	(C)
Confusion	(C or V-B)
Impaired hearing	(C or V-B)
Syncope	(C or V-B)
Convulsions	(C or V-B)
Behavioral change	(C)
Transient cranial nerve palsies	(V-B)
Drop attacks	(V-B)

C = Carotid Arterial Distribution
V-B = Vertebral-Basilar Arterial Distribution

TABLE 2
Associated Diseases in Stroke Patients

1) Hypertension	75.8%
2) Hypothyroidism	38%
3) Diabetes	31%
4) Myocardial Infarct	10%
5) Arteriosclerotic Heart Disease	51.7%
6) Rheumatic Heart Disease	4%
7) Hypercholesterolemia	44.7%
8) Postural Hypotension	16%
9) Gout or Hyperuricemia	33%
10) Peripheral Arteriosclerotic Ischemia	5%
11) Syphilis	5%
12) Anemia	13.1%
13) Polycythemia	1.5%

Illustrative Case History

A manager of a steel plant at age 42 suffered occlusion of one vertebral artery. The opposite vertebral and both carotid arteries were severely stenosed as shown by arteriography. He presented with severe ataxia, dysarthria, and hyperuricemia. Blood cholesterol and glucose tolerance tests were normal and hypertension was absent. The association of gout and atherosclerosis of the coronary vessels is well established;[4] this was the only metabolic disorder to account for his premature cerebral atherosclerosis. He is back at his employment and free of symptoms, following bilateral carotid endarterectomy. Post-operative arteriography one year after surgery shows excellent restitution of flow through both carotid arteries.

Recently twelve patients have been examined with adrenal cortical insufficiency, severe postural hypotension, and neurological deficit, due to cerebral arteriosclerosis proven by arteriography. The adrenal insufficiency proved to be secondary to selective pituitary insufficiency.[5] In all cases therapy with 20 mg. of hydrocortisone daily abolished the postural hypotension and the neurological deficit, which had been refractory to oral vasodepressor drugs.

Identity of Vascular Obstruction

While clinical and laboratory data, in the majority of cases, are sufficient to classify the disorder correctly, objective definition of any vascular obstruction is essential before consideration of surgical reconstruction is possible. Furthermore, if anticoagulant or fibrinolytic therapy is to be considered, cerebral hemorrhage should be excluded.

Disadvantages of Arteriography

At the present time visualization of the cerebral blood supply from the aortic arch to the brain is the objective diagnostic method of choice, but there are three disadvantages to its present use: (1) complications using standard techniques of arteriography occur in 3-4% of cases, (2) obstructive lesions may be present in vessels that are too small to visualize, and (3) small hemorrhagic lesions may not be recognized.

Hoping to solve these problems, attempts have been made to improve techniques of arteriography and to develop a harmless screening method which might assist in limiting arteriography to those patients with accessible lesions in the neck.

Improved Methods of Arteriography

Improvements in technic will reduce the complications of arteriography. In order to visualize the cervico-cerebral circulation, the number of vessels punctured has now been reduced to two or three. Bilateral retrograde brachial artery injection is routinely performed with a Seldinger needle[1-4] on the right and a Rochester needle[5] on the left. An Amplatz pressure injector is used, set at 50 lbs. pressure and the dye warmed to 35° C.

Sedation

Premedication prior to arteriography may significantly reduce complications. It is now our practice to use Phenergan 25 mg., Atropine 0.4 mg. and Dilantin 100 mg. by intramuscular injection prior to carotid arteriography. With the use of Dilantin only one seizure has occurred in the last 150 cases in which all four cerebral vessels have been examined by arteriography, and in that single case the seizure occurred twelve hours after arteriography.

Carbon Dioxide and Oxygen

Inhalation with 5% carbon dioxide and oxygen for three to five minutes immediately prior to arteriography permits better visualization of the cerebral vessels and decreases the hazard of the transit of dye through the cerebrum in patients with marginal cerebral circulation.

The Dyes

To compare the two dyes, Conray (Mallinkrodt) and Renograffin were used alternately in the same artery as contrast media. Renograffin was found to be most satisfactory as judged by the patients' subjective statements, absence of electroencephalogram change (which was monitored during arteriography), and opacification of vessels. In two subjects in whom Conray was used during brachial arteriography, transient occipitoparietal slowing appeared in the electroencephalogram shortly after the injection.

Brachial Injection

Direct puncture of the cerebral vessels in the neck is potentially hazardous, since this may result in subintimal injection, dissecting aneurysm, dislodgement of thrombi, or atherosclerotic plaques and injury to the intima. For this reason direct puncture of the carotid and vertebral arteries has been avoided as much as possible. Blood pressure cuffs were placed about the left arm and both thighs, and were inflated above arterial pressure during brachial injection. Twelve exposures were then made at intervals of 0.5 seconds or less, using a Sanchez-Perez or Sjonander rapid cassette changer. Rapid seriograms permit accurate visualization of the entire vascular tree from arterial to venous phase, as well as accurate measurement of cerebral circulation time. With retrograde injection of the right brachial artery, the right brachial and carotid arteries can always be visualized throughout their entire course. If the catheter is then passed into the aortic arch, the left common carotid artery can be visualized in twenty-five per cent of cases, also the left vertebral artery if it arises from the aorta. Rapid seriograms are necessary, since opacification of the left carotid artery may be very brief. Left retrograde brachial arteriogram always permits visualization of the left vertebral artery, unless it arises from the aorta. In about 75% of cases, the left common carotid artery is not visualized, and direct puncture of the left carotid must be performed. The Cournand needle used has a blunt cannula and minimizes the danger of intramural injection.

Using the above premedication and technics, there have been no immediate seizures and only two nonfatal neurological complications in the last 100 total cervicocerebral arteriograms performed on subjects with stroke.

Cerebral Circulation Time in Stroke

Routine measurement of cerebral circulation time has aided greatly in the diagnostic precision of angiography, particularly in strokes. In areas of severe arterial stenosis and invariably in regions of occlusion, the local transit time of the bolus of dye through the brain is prolonged.

Influence of Associated Diseases

More important, however, is the observation that in subjects with hypertension, diabetes, and severe arteriosclerosis, the time of the circulation is prolonged throughout the entire brain. When such individuals developed focal neurologic deficit, more marked slowing of the time of circulation through the brain was present during the acute phase and tended to revert toward normal as the patient improved. Furthermore, the slowing of the circulation in acute stroke was often found in the absence of recognizable occlusion of major cerebral vessels. The delay appeared to be in the smaller arteries of the brain measuring 500 mu. and less. Despite localized neurological deficit, the slowing was often more extensive than might be anticipated from the neurological findings. Presumably the slowed circulation is caused by multiple thrombi in the small vessels or by embolic fragments dislodged from the heart or proximal vessels. A contributory factor is the metabolic depression which occurs in cerebral infarction with reduction of carbon dioxide production by damaged brain. Carbon dioxide is a potent cerebrovasodilator and thus tends to decrease cerebrovascular resistance.

Measurement of Cerebral Circulation Time by Radioisotopes

At the present time a technic is being investigated which does not require arterial puncture. This is a modification of technics originally suggested for measurement of cerebral blood flow[6-7] and is being investigated for screening, diagnosis, and localization of cerebrovascular lesions. Multiple collimators are placed over the frontal, temporal and occipital regions of the skull, over the carotid bifurcation in the neck, and over the heart. A bolus containing five to ten microcurie of radioactive serum albumin or radioactive hippuran is injected intravenously. Circulation times are simultaneously recorded on a polygraph from each collimator by means of quantitative counters, amplifiers, and pens.

In an area of ischemia, such as follows middle cerebral occlusion, there is a delay in the passage of radioactive material through the ischemic portion of brain. Possibly a delay in passage through the neck might be demonstrated that would suggest an extracranial site of obstruction. The technique is being evaluated to determine whether the occlusion is in the neck (and potentially amenable to surgery) or in the cerebral vessels themselves.

Clotting Diathesis in the Progressive Stroke

One hundred cases of acute progressive stroke have now been evaluated with streptokinase or fibrinolysin therapy, using double blind or randomized control. Cases with cerebral hemorrhage, blood in the cerebrospinal fluid, and systolic blood pressure above 180 mm Hg. were excluded. The control series were treated with anticoagulants alone; the treated cases received intravenous fibrinolysin or steptokinase. Results so far are disappointing except some benefit by fibrinolysin for the older age group.[8] When streptokinase is used, one-quarter the dose prediction test is used and careful clinical and biochemical control of treatment is essential.[9] Prednisone or hydrocortisone is given concurrently to minimize any allergic reaction. Serial clotting studies have been made on all patients.

The results obtained in the control series of cases has proven to be as interesting as in the treated group. It was apparent that a clotting diathesis was present in the acute progressive cerebral thrombosis. Significant differences were found in the clotting properties of the blood in those patients that recovered when compared with those that died. In the cases proven to have a good prognosis, there was evidence of more active fibrinolysis; in the untreated cases, this was spontaneous (presumably due to the stress). In the treated group the fibrinolysis activity was due to the administration of the enzyme; in both the treated and untreated groups that had a good prognosis, antiplasmin was reduced, profibrinolysin was reduced, and fibrinogen, which was initially elevated, decreased (Fig. 1).

In acute strokes the fibrinogen was usually

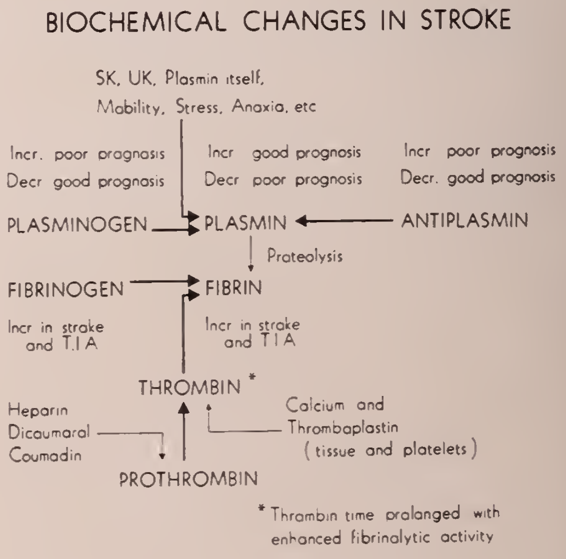
BIOCHEMICAL CHANGES IN STROKE
SK, UK, Plasmin itself,
Mobility, Stress, Anoxia, etc
Incr. poor prognosis
Decr good prognosis
Incr good prognosis
Decr poor prognosis
Incr poor prognosis
Decr. good prognosis
PLASMINOGEN
PLASMIN
ANTIPLASMIN
Proteolysis
FIBRINOGEN
FIBRIN
Incr in stroke and T.I.A
Incr in stroke and T.I.A
THROMBIN *
Heparin
Dicoumarol
Coumadin
Calcium and
Thromboplastin
(tissue and platelets)
PROTHROMBIN
* Thrombin time prolonged with enhanced fibrinolytic activity

Fig. 1

elevated as was specific activity of plasminogen, the ratio of plasminogen to total protein. In patients with a good prognosis this ratio fell; in the patients who died or whose neurological defect worsened, the plasminogen to total protein ratio rose, as did the fibrinogen and antiplasmin levels.

Serial arteriograms repeated at intervals correlated well with the coagulation studies. In those patients treated with fibrinolytic agents or who showed spontaneous increase of fibrinolytic activity, lysis of clots was often shown to have occurred.

Studies of Cerebral Blood Flow and Metabolism in the Acute Stroke

Paired arterial and jugular venous blood samples have been made in forty patients with acute stroke and compared with the electroencephalogram findings, and in many cases the arm to retina circulation times were also measured.[10]

Oxygen and Carbon Dioxide Tension

In many, these biochemical studies were repeated at intervals of one to two days. In general, the arterial oxygen tension and carbon dioxide tension were low in acute strokes with a moderate alkalosis present. This is believed to be due to respiratory depression and pulmonary atelectasis, commonly present in the acute stroke. There was a narrowed arterial-jugular oxygen tension and glucose difference. These changes are believed to indicate cerebral metabolic depression in acute cerebral infarction, since in many cases the cerebral circulation was measured and found to be slowed.

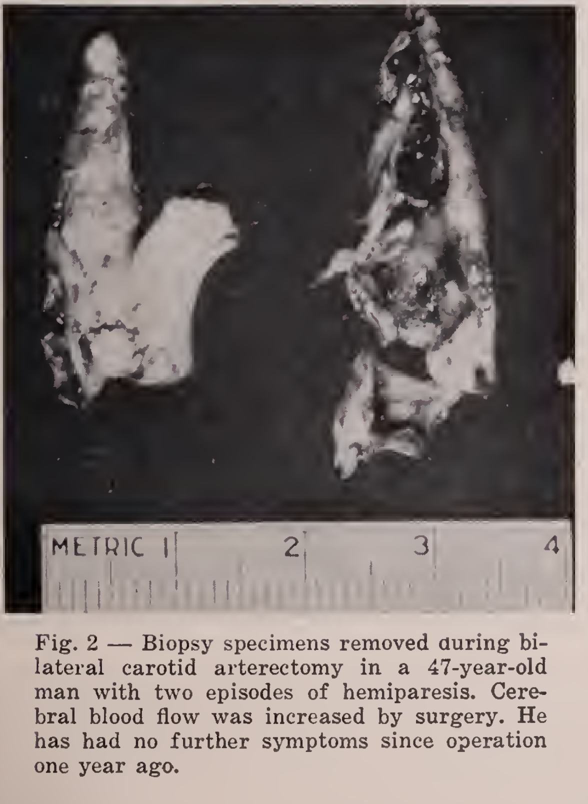

Fig. 2 — Biopsy specimens removed during bilateral carotid arterectomy in a 47-year-old man with two episodes of hemiparesis. Cerebral blood flow was increased by surgery. He has had no further symptoms since operation one year ago.

Value of Oxygen

More recently, cerebral blood flow and metabolism have been continuously recorded together with the electroencephalogram in acute strokes. A catheter was inserted into the jugular vein and the jugular venous blood was drawn through a manifold in which electrodes were inserted to measure oxygen tension, carbon dioxide tension, hydrogen ion concentration, sodium and potassium. Cerebral blood flow was monitored by thermodilution and thermoelectric methods, and blood pressure, electrocardiogram, electroencephalogram, and alveolar oxygen tension were also recorded on the graph.

Such measurements have established that administration of 100% oxygen in the acute stroke increases the oxygen available to the brain, and intermittent breathing of a mixture of 95% O_2 and 5% CO_2 increases cerebral blood flow and oxygen available to an infarcted brain. Treatment of strokes by these means often results in clinical and electroencephalogram improvement.

Low Molecular Weight Dextran

Low molecular weight dextran improved cerebral circulation in some strokes; and vasodilator drugs have had useful effect to date. A fall in blood pressure or elevation of the head by tilting 45° decreases cerebral blood flow and oxygen availability. Carotid compression in young individuals does not significantly alter cerebral blood flow or metabolism; but in some patients with cerebral atherosclerosis, jugular oxygen tension and carbon dioxide tension decreased with syncope and electroencephalogram change.

Cerebral Blood Flow Before and After Surgical Treatment of Strokes

Cerebral blood flow has been directly measured in monkeys and man by applying electromagnetic flowmeters to the jugular veins. The studies in man were made in the operating room during thyroidectomy or before and after surgical reconstruction of obstructed carotid arteries in the neck (Fig. 2). Direct measurement of jugular blood flow by this method gave normal values of 70 ml./100 G brain per minute, which confirm measurements made by Kety and Schmidt using an indirect method (the Fick principle). In cases of stroke, values for cerebral blood flow were low, averaging 60 ml./100 G brain per minute; but after surgical reconstruction, there was a statistically significant increase in cerebral blood flow to over 80 ml./100 G/min.[11]

Results in Treatment of Stroke

Surgery

It may be some time before carefully controlled data is available concerning the value of surgical treatment of stroke. About 75% of patients with stroke have surgically accessible arterial lesions. Ninety patients have now been "randomized" in a controlled manner for carotid and vertebral reconstruction in our department. Equal groups with surgically accessible lesions were selected for surgical or medical treatment in an entirely random manner. Further follow-up is needed; but it is apparent that anatomical restitution of atherosclerotic vessels in the neck can be achieved by surgery; cerebral blood flow is measurably increased thereby; and, in some patients, symptoms and signs were improved or abolished.

Medical Therapy

Streptokinase is disappointing but may dissolve clots if given within the first three days of onset of a stroke. Anticoagulant therapy is useful in abolishing repeated transient ischemic attacks.

After careful diagnostic evaluation many stroke patients respond well to general medical means, such as treatment of anemia, polycythemia, pituitary-adrenal insufficiency, cardiac disorders, and the like. Oxygen, and 5% CO_2 and oxygen have value in the treatment of severe cerebral ischemia and infarction. Cerebral blood flow in patients with stroke can be increased by certain vasodilator drugs, provided the blood pressure is not lowered. The most useful drug studied to date has been papaverine.

Summary

Recent investigations of cerebral blood flow, metabolism, and biochemical changes in strokes have been reviewed. In the light of this new information, the value of certain types of medical and surgical treatment of occlusive cerebrovascular disease has been discussed.

In man, the extreme efficiency of the healthy cerebral collateral circulation was demonstrated. This is decreased by cerebral atherosclerosis; but cerebral blood flow is increased following endarterectomy for stenotic lesions of the carotid vessels in the neck.

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St. John's Evil

In medieval times St. John became the patron saint of epileptics and was invoked for protection against the disease.

Historically revealing light is shed on the subject by Riesman in his "Medicine in the Middle Ages":

"Epilepsy was treated in England by the wearing of cramp rings. Cramp rings were for the most part made of silver acquired for the communion service. Many were made of coffin nails or even pieces of navel string. The supposed curative property of these rings dates back to a legendary ring of Edward the Confessor. The story is that Edward while dedicating a church to St. John the Evangelist gave his ring to a begger who asked for alms. The beggar was revealed as St. John himself. This legend explains the synonym of epilepsy, *morbus sancti ionnis.*"*

Also from the same legend was derived the more intriguing and durable synonym for epilepsy — St. John's evil.

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*Riesman, David, M.D.: The Story of Medicine in the Middle Ages, p. 249.

BOURNEVILLE'S SYNDROME

(Tuberous Sclerosis)

Tuberous sclerosis is a disease characterized by a clinical triad of mental deficiency, epilepsy, and adenoma sebaceum. It is thought to be heredofamilial and is more often observed in females in complete form as the syndrome may occur. The butterfly-shaped rash on the nose and cheeks and the X-ray findings in the skull revealing calcification within the cranium are the most conspicuous findings on clinical examination. Tumors of the retina, kidneys, and heart are often present. Spina bifida, polydactylia, and a cleft or high-arched palate may be evident. Multiple skin nodules similar to those seen in von Recklinghausen's disease may appear. The kidney tumor, with multiple bilateral benign tumors of the kidney, is found in more than half the cases. Whether the condition is primarily neoplastic or an expression of disordered development of early embryonic life has not been determined.

No specific treatment is known.

Textbook of Neurology, H. Houston Merritt, M.D., Philadelphia 1963, page 440

See What's Your Diagnosis Page 254.

Ours is a world of nuclear giants and ethical infants.—Gen. Omar Bradley

Intermittent Positive Pressure Breathing

WILLIAM F. MILLER, M.D.**
Dallas, Texas

MODERN TECHNOLOGICAL and physiological advances have not only provided us with an improved ability to recognize and understand the nature of disordered breathing, but also provided us with a variety of mechanical devices for treating many of these disorders.

Intermittent positive pressure breathing apparatuses are basically mechanical devices for providing either assisted or controlled ventilation. In some respects the proper application of these devices is technically complicated, largely because the effective utilization of intermittent positive pressure breathing equipment depends on the complex interplay of factors relating not only to the instrument but also to the respiratory system of the patient.

Indications

The indications for intermittent positive pressure breathing can be considered as follows:

1. To improve the distribution of ventilation, that is, to produce slow deep breathing.
2. To relieve the work of breathing which is the principal cause of dyspnea.
3. To correct hypoventilation and the subsequent carbon dioxide retention.
4. To provide simple mechanical ventilation for the apneic patient.
5. To administer high concentrations of oxygen in the neighborhood of 100% to individuals with severe ventilation-perfusion disturbances, such as severe pneumonia or pulmonary edema.

The most frequent, but not necessarily the most important, application of intermittent positive pressure breathing is for convenient administration of bronchodilator drugs by aerosol. Most patients receiving bronchodi-

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These studies were supported in part by USPHS grant H-5167.

Indications and Methods of Application*

lator drugs intermittently would probably respond to a bronchodilator aersol administered without positive pressure; this would be particularly true if they were properly instructed in slow deep breathing with an inspiratory pause after inhalation of the aerosol.

Patients with severe ventilatory insufficiency or large quantities of obstructing secretions will find intermittent positive pressure a more comfortable way of taking aerosol bronchodilator therapy, and will generally get better results from individual treatment because they actually will be breathing the aerosol in a more effective manner.

Establishing Effective Airway

The first step in the proper application of intermittent positive pressure breathing devices is the establishment of an adequately controlled airway. Generally speaking, intermittent positive pressure breathing can be administered for only relatively short periods of time by a mask or mouthpiece. For the

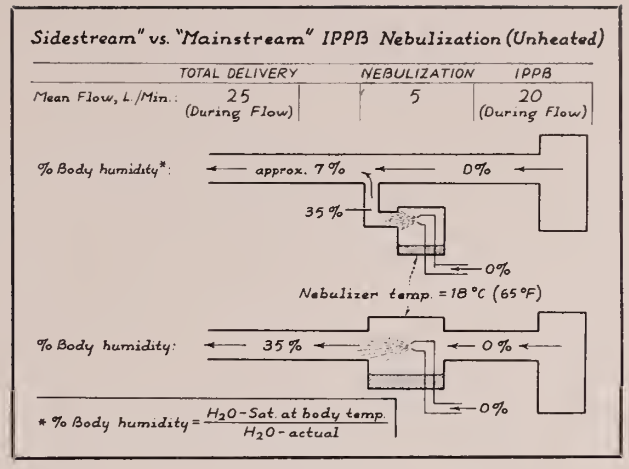
Sidestream" vs. "Mainstream" IPPB Nebulization (Unheated)
TOTAL DELIVERY
NEBULIZATION
IPPB
Mean Flow, L./Min.:
25 (During Flow)
5
20 (During Flow)
% Body humidity*:
approx. 7 %
0%
35 %
0%
Nebulizer temp. = 18 °C (65 °F)
% Body humidity:
35 %
0 %
0%
* % Body humidity = H₂O-Sat. at body temp. / H₂O-actual

Fig. 1

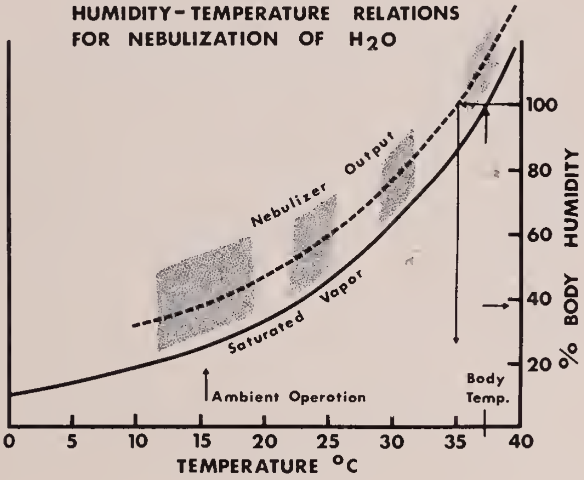

Fig. 2

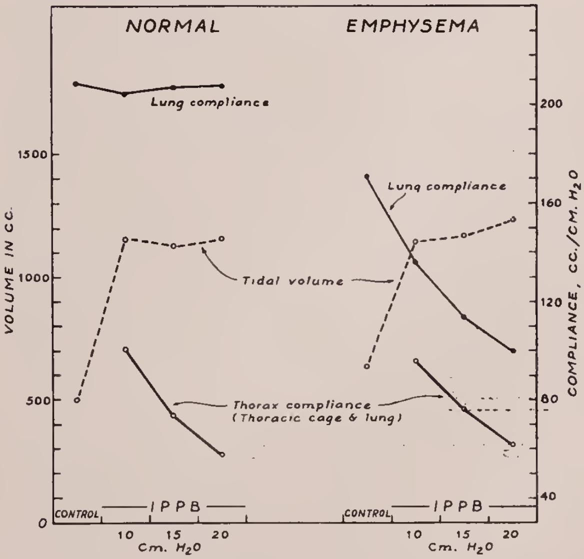

Fig. 3

patient who is fully cooperative, and who needs to cough and expectorate frequently, the mouthpiece is usually most convenient. Some patients prefer a mouthpiece because they dislike having their face enclosed in a mask. The mask on the other hand can be utilized for the marginally co-operative patient, but after twenty-four to forty-eight hours of use, necrosis across the bridge of the nose can be prevented only with great care.

The major disadvantage of utilizing a mask for the patient who is not completely alert and co-operative is the danger of producing gastric distention due to air being forced into the stomach. In those situations where it may be desirable to persist with the mask as a means of administration, some degree of control over gastric distention can be accomplished by the simultaneous insertion of a gastric tube allowing free escape of air. It should be emphasized that, when this method is employed, the stomach should first be aspirated to remove any residual gastric content, because the danger of regurgitation is enhanced in the presence of a stomach tube. In those situations where the patient is not adequately co-operative because of some alteration in his mental state, an endotracheal tube inserted either through the oral pharynx or nasal pharynx can be utilized for periods up to 48 hours.

Most people feel that tubes inserted through the nasal pharynx are better tolerated than those inserted through the oral pharynx. Such tubes should have inflatable cuffs. Cuffs of the closed type should be inflated only with minimal pressure to permit successful operation of the intermittent positive pressure breathing machine. In many instances moderate leaks are not only well tolerated but desirable. If it seems likely that ventilatory assistance or controlled ventilation is necessary for a period longer then 48 hours, a tracheostomy should be performed.

The same consideration mentioned in regard to the cuffed endotracheal tube also applies to the cuffed tracheostomy tube. The cuff should be deflated as frequently as possible for short periods of time. So long as these considerations are applied, difficulties will not arise with utilization of indwelling tracheal cuffs.

Ventilator Devices

Almost any of the available apparatuses can be applied to the patient with an essentially normal lung in a satisfactory manner. Proper selection of the ventilator for the more difficult patient requires a thorough knowledge of the functioning characteristics of the various apparatuses. Basically ventilators may be classified as one of two types:

1. Pressure-controlled, that is, pressure is the machine-limiting-factor to volume ventilation.
2. Volume-controlled, in which case a predetermined volume is delivered to the patient irrespective of the pressure required.

In a recent survey it was apparent that the two instruments most widely used are the Bennett and the Bird. They are representative of the two types of pressure controlled units. All others including the Dotco, Monaghan, MSA and Emerson are basically similar.

The Bennett Instrument

The Bennett PR 1 model is the only Bennett unit capable of functioning satisfactorily as a controlled ventilator as well as a ventilatory assister. Other models function essentially as assisters only. The characteristics of the PR 1 may be listed as follows:

1. An inspiratory sensitivity control essential to adjusting the amount of effort required to initiate inspiration. One may wish to vary this under certain circumstances in order to regulate the respiratory pattern.

2. A pneumatic timer which controls both phases of respiration. When the automatic timer is operating, the instrument is largely slaved to the timing device, but since it is pneumatic, flow and pressure characteristics are not significantly disturbed.

With the automatic timer the instrument will operate with a sizable leak.

The instrument will not signal obstruction when operating on the automatic timer since the incidence of inspiration and expiration are not as much affected by pressure and volume relationships under automatic cycling control. Thus, only careful observation or measurement of tidal ventilation will insure adequate patient ventilation.

3. Continuous nebulization characteristics of this instrument may interfere with patient's cycling and obligate the system to a higher oxygen concentration in spite of air mix. Intermittent nebulization is available on request.

4. The initial inspiratory flow of this unit is essentially proportional to the pressure setting, and flow automatically decreases with increasing back pressure, resulting in a very smooth type of operation. The unit has characteristically a preset low flow cutoff which means that when cycled into inspiration it tends to maintain inspiration until the rate of flow into the patient drops to a level of, at times, less than 5 L./min. when the automatic timer is not operating. However, because of this, the unit becomes very sensitive to leaks and will not cut off unless an airtight system is provided, or some auxiliary flow is added.

5. The air mix function of this unit is consistent even at low flows, since the high pressure oxygen flow also diminishes as the cutoff pressure is approached.

The Bird Mark VII Instrument

The characteristics of the Bird Mark VII respirator are as follows:

1. It also has inspiratory sensitivity control.

2. It has a pneumatic timer which controls expiration only. Therefore, the system will be sensitive to leaks, when operating at low flow. Moreover, the presence of leaks may obscure the presence of obstruction regardless of whether the automatic timer is in operation or not. That is to say, the cycling of the machine is no guarantee that the patient is being ventilated. The system becomes sensitive to obstruction only at relatively higher flow settings in the absence of leaks.

3. On 100 per cent oxygen the instantaneous flow rate is relatively low, so that the apprehensive patient with a rapid respira-

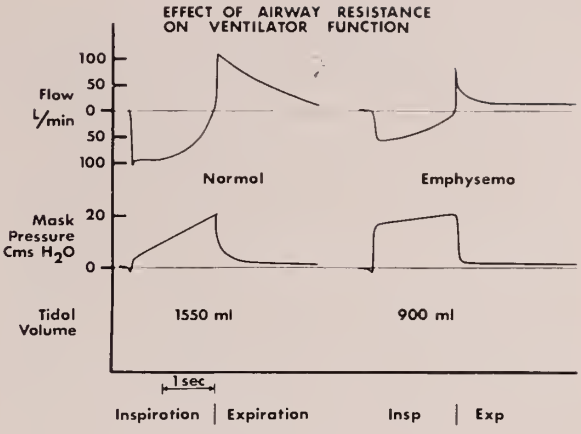

Fig. 4

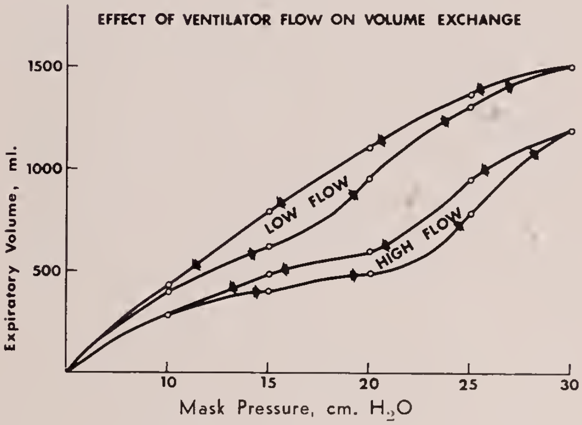

Fig. 5

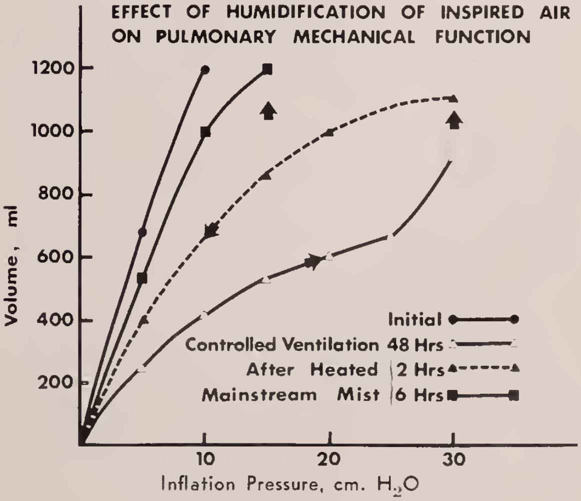

Fig. 6

tory rate may experience some difficulty in achieving ventilatory assistance early in inspiration under these circumstances. This may be corrected in part by using high flows or by using a continuous nebulizer flow at a fairly high level.

4. Nebulization with this unit is basically intermittent but may be continuous by choice.

5. The air mix, like all such units, works best at high flows and poorer at low flows, which are often selected by choice with this unit.

Other Ventilator Instruments

Most of the other ventilatory assisters are pressure controlled and, although somewhat variable in initial cost, are functionally basically the same. They tend to operate at higher flows, are very sensitive to the presence of airway obstruction, have pneumatic timers which limit expiration only, and are variable in the facility with which they can be adjusted to different patient situations. The Dotco pneumatic balance unit is most versatile of these, but likewise the most difficult for the inexperienced to operate properly.

Volume Control Ventilator

The most widely used volume control ventilator in this country is the Mörch Pump, which is a piston pump with a stroke control to determine the volume delivered. One advantage is that with an airtight system it insures a specific volume in spite of transient lung changes. One disadvantage is the inadequacy of the humidification system, which could be corrected by using a heated, main-stream humidifier. This type of pump will not signal obstruction or airleak unless equipped with an alarm system to indicate when pressure has risen or fallen beyond certain limits. Such provisions are available on the Engström unit.

Humidification System

Having selected a ventilator, the next consideration is the adequacy of the humidification system to meet the needs of the circumstances at hand. Most of the pressure controlled intermittent positive pressure breathing machines are equipped with side stream nebulizers illustrated in the upper part of Figure 1. It is apparent that this type of system contributes a very small amount of moisture to an essentially dry gas, resulting in a very low water content in the air delivered to the patient, and if continued for any period of time will unquestionably have a drying effect. The phrase "drying up the secretions" is often erroneously used in connection with pulmonary problems, and it should be categorically stated that there is never any indication for physically "drying up" bronchopulmonary fluid. Moisture is essential in the lungs, both for normal mechanical and gas exchange function; by contrast, accumulated viscous exudate is undesirable.

Abnormal Fluid Accumulation

Abnormal accumulations of fluid in the lungs consist of material of high viscosity and high surface tension, which greatly interferes with the mechanics of ventilation. It is virtually impossible to deliver excessive quantities of fluid by aerosol to patients, because the amount delivered is negligible and the retention ratio is very low (30%) in relation to the reabsorptive capacity of the lungs. If a patient has difficulty with excessive fluid in the lung, this is due largely to the character of the fluid which interferes with its absorption and the underlying lung disease which interferes with the normally very effective reabsorptive processes of the lung or the effective expectoration of excess secretions.

Adequate Humidification

In any event, when assisted ventilation is to be administered to a patient for any period of time, adequate humidification of the air must be provided. A mainstream system of nebulization, as illustrated on the bottom part of Figure 1, indicates a considerable improvement in humidification that can be achieved by passing the mainstream of air from the breathing pump through the nebulizer system. A level of water content of 35 per cent of body humidity restores the inspired air only to a tolerable level, comparable to humid atmospheric air. This does not constitute high humidity therapy and will not contribute significantly to humidification of the respiratory tract in those circumstances where thick exudate indicates the necessity for high level humidification. This can only be accomplished by the addition of heat to the system in order to increase the content of water that can be carried in the inspired air. When ventilatory assistance is applied directly to the trachea, every attempt should be made to maintain homeostasis. Normally, air arriving at the trachea is 100 per cent humidified near-body temperature. Such characteristics of inspired air can only be achieved by the use of a mainstream, heated nebulizer unit. It is often stated that people get by with using less desirable systems when applying ventilatory assistance through a trachea. Getting by is not proof that such practice is correct.

Inadequate Humidification

Inadequate humidification is responsible for many common complications of prolonged mechanical ventilation.

The basic considerations of humidification by nebulization are considered in Figure 2 in which the relationship between temperature and humidity (expressed as vapor humidity) is indicated by the solid line which represents 100 per cent relative humidity at the respective temperatures shown along the horizontal axis. The water or humidity contributed to the system by the fog delivered from the nebulizer is indicated by the dashed line. The shaded areas represent the scatter of observations made on many nebulizers operated at different temperatures. It can be clearly seen that, the fog from a nebulizer contributes only a very small part to the total water content delivered to the patient, and that under normal ambient operating conditions the humidity of the inspired air would be low with respect to body humidity. Thus, it is apparent that the temperature of the system, that is, the solution temperature, must be raised so that the air flow delivered is near body temperature in order to achieve full humidification. The solutions used in these units vary with the circumstances under treatment. For simple humidification water alone is adequate. For mobilizing secretions or exudate, detergent solutions such as Tergemist^R or Alevaire^R may offer some advantage over saline and propylene glycol (2-5 per cent) mixtures. The latter is much less expensive, however.

The Ventilating Pressure

It can be categorically stated that there is no arbitrary pressure which should be selected. Ordinarily speaking, when intermittent positive pressure breathing machines are being utilized for bronchodilator therapy in ambulatory patients, the arbitrary setting of 15 to 20 centimeters of water pressure is satisfactory; under these circumstances, this is adequate pressure to provide the patient with a somewhat greater than normal tidal volume and is a level of pressure easily tolerated by the patient. In most instances where intermittent positive pressure breathing is being used, the patient has mechanical respiratory difficulty, either due to restriction of the respiratory apparatus or obstruction of the airways. This means that increased amounts of force are necessary in order to achieve adequate ventilation. In a normal individual 10 centimeters of water pressure is usually adequate to produce an inspiratory volume of 1200 to 1600 cc.; in patients with respiratory difficulty, 10 centimeters of water pressure may produce no more than 200 to 300 cc. volume exchange.

Overexpansion

It is important to realize that there is virtually no danger of overexpansion of the chest in a conscious patient. Figure 3 illustrates the point effectively. Here the volume plotted against pressure is shown in the dashed line. In order to demonstrate the limiting factor to further volume expansion, lung compliance and total compliance are shown in the solid line. Lung compliance did not change, whereas total compliance fell, indicating that further expansion was being resisted by the thoracic cage and not by the lungs. This was a completely relaxed trained subject. In patients this effect is even more noticeable. Thus, the lung is well protected against overdistention in the intact person. By contrast, on the right is pictured data from a patient with severe emphysema. Here the lung compliance declines and the total compliance declines in parallel. The lung and thorax have reached the limit of distensibility and are limiting further expansion. Thus, except in the presence of severe inspiratory airway obstruction, relatively low pressures should be adequate for patients with emphysema.

By contrast, in the patient with pulmonary edema, or severe pulmonary infection, much higher pressures are required because of the marked reduction in compliance and very marked increases in airway resistance. The compliance or distensibility of the lung will be decreased in proportion to the reduction in alveolar volume. The principal mechanism of volume reduction is filling airways with viscid fluid, effectively eliminating lung units. In addition, interstitial congestion aggravates the reduction in compliance caused by decreasing lung volume.

Airway Resistance

Another factor causing severe increased effort of breathing in pulmonary edema is increased airway resistance. During inspiration, the patient usually requires 40-50 cm. of water at the onset of inspiration just to overcome air flow resistance. In addition 20 cm. or more are usually required to overcome increased elastic recoil resulting from low lung compliance. In practice that amount of assisting pressure which will produce effective ventilatory assistance should be used, otherwise one cannot expect to alleviate respiratory distress. The frequent practice of utilizing 15-20 cm. of water on the intermittent positive pressure breathing machine in patients with pulmonary edema obviously will not alleviate respiratory distress and may only frustate the patient, making him rebel against the treatment. We always employ bronchodilator and detergent solution in the nebulizer. We rarely find addition of alcohol as an antifoam necessary.

Ventilator Flows vs. Airway Resistance

Figure 4 shows the inspiratory-expiratory flow curves and the mask pressure curves on a normal person and a patient with bronchitis and emphysema using a 20 cm. intermittent positive pressure breathing pressure at a fairly high flow. It is apparent that the high airway resistance in the patient causes the mask pressure to rise to the limiting pressure before the same volume exchange is achieved as in the normal when high flows are used. This points up the role of controlled low flow in the presence of high airway resistance.

Figure 5 emphasizes this point further. Here pressure is plotted against volume with an intermittent positive pressure breathing device operating at low flow in the upper curves and high flows in the lower curves in a patient with acute diffuse obstructive disease. It is apparent that greater volume exchange is achieved at low flow.

Ventilation Control

These curves also serve to illustrate how the mechanical properties of the lung can be studied at the bedside with simple tools. The pressures are observed on the intermittent positive pressure breathing machine at stepwise increments of pressure increase while the volume exhaled is collected from the expiratory valve in a spirometer or other ventilation meter. The changes in the slope of these curves as pressure is being increased indicate that lung units are opening at higher pressures. The slope of the descending curve in each instance is higher than the ascending curve, illustrating the hysteresis effect resulting from the fact that at the higher pressures lung units open increasing the compliance of the system.

Figure 6 illustrates the manner in which this technic can be utilized to demonstrate certain other aspects of prolonged assisted or controlled ventilation. This is data from a paralyzed patient who exhibited normal overall pressure volume relationships initially; but a progressive deterioration was observed from the top to the bottom curve, presumably as a result of continuous ventilation at usually prescribed tidal volumes which will maintain gas exchange initially but will not prevent closure of lung units. Recovery of function was achieved with adequate humidification and deep breathing. Such closure of lung units sets the stage for more serious pulmonary complications such as poor distribution of ventilation and hypoxia. In some situations the tendency for closure of lung units to recur is so persistent that it becomes necessary to ventilate patients constantly at large tidal volumes in order to maintain satisfactory distribution of ventilation. Large tidal exchange in turn may lead to alveolar hyperventilation with respect to CO_2 as illustrated in Table 1. The solution to this problem is the addition of dead space as shown in the third column. This is accomplished by inserting additional short flex tubes between the patient and the exhalation valve. The proper amount of dead space can only be determined by trials.

Adequate control of patients on prolonged mechanical ventilation can be achieved only by careful patient observation correlated with volume ventilation and blood gas studies.

Inspired Oxygen Control

The problem of regulation of oxygen concentration during intermittent positive pressure breathing therapy is often discussed with proper concern for avoiding unnecessarily high levels of oxygen. This is especially true in severe diffuse obstructive disorders where obstruction and high oxygen increases the likelihood of rapid reabsorption and atelectasis.

It is usually not well understood that air dilutors do not provide, except under special circumstances, the concentrations of oxygen stated by the manufacturers, because the percentage of air dilution is inversely proportional to the back pressure or mask pressure and directly proportional to the flow. Thus 40 per cent oxygen is delivered at the very beginning of inspiration if the back pressure is low and the flow is relatively high. Other factors contribute further to increases in ultimate oxygen concentration. The nebulizers operate from line pressure oxygen. If the patient is being ventilated at a tidal volume of 700 ml. or less with continuous flow nebulizers on the machine, he may be receiving 100 per cent oxygen even with an air mix intermittent positive pressure breathing, because the 600-800 ml. of tubing and nebulizer space is filled with 100 per cent oxygen. If the nebulizers operate intermittently the resulting oxygen concentration will be lower, but no lower than about 65 per cent oxygen.

Summary

Certain aspects of the physiological application of intermittent positive pressure breathing have been considered. Emphasis has been placed on recognition of the fact that proper assisted or controlled ventilation can only be achieved with due consideration of the mechanical principles of the apparatus and the physiological characteristics of the patient's respiratory apparatus. Critical observations of the patient are necessary at all times to insure adequate ventilation.

Acknowledgment

Dr. Ivan E. Cushing contributed data and other helpful suggestions.

The Barber Surgeon

The barber's pole began its career in the Middle Ages, when the art of surgery and the trade of barber were combined. Blood-letting was then a great cure-all: a vein in the arm was opened, and the patient was given a stick or pole to grasp tightly, thus making the blood flow more freely. When not in use, the stick was hung outside the shop, with a white bandage wound around it in a spiral, ready for use — indicating that a surgeon was available. But the sight of the gory pole was discouraging to the squeamish, so in time the barbers displayed a pole painted red and white, instead of that actually used in the operation.—Marion Nicholl's "Handwrought Ancestors"

Why not go out on a limb? Isn't that where the fruit is?—Frank Scully

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Rest is for the dead.—Thomas Carlyle

Paracelsus

Physician, chemist, charlatan: with these three nouns the Encyclopedia Americana characterizes Paracelsus.

That life processes are chemical; that Nature closely observed is the only reliable and authentic teacher: these two unorthodox declarations by a Swiss doctor in the early 16th century constituted medical heresy.

The revolutionary, flamboyant, and controversial figure responsible for these categorical statements was born Auriolus Theophrastus Bombastus von Hohenheim in 1493, who studied medicine under his conservative physician father and later at the equally conservative University of Basel. Rebelling, however, against learning from secondhand, authoritarian sources and desiring firsthand, personal experience, Paracelsus renounced school and betook himself to the Tyrol mine area to observe what actually happened to men's bodies in their raw, day-to-day work lives. He even journeyed to the Far East, where he became familiar with some fabulous remedies with which to astound and disconcert his colleagues when he subsequently returned to Basel, as he did—first to become town physician and later to lecture at the University.

On his first appearance in the classroom he immediately committed lese majesty by dispensing with all Latin textbooks and proceeding to lecture in German from his own vast store of self-acquired knowledge.

On one occasion when the students were congregated around a festive bonfire on the college grounds, Paracelsus strode dramatically to the scene with books by Galen and Avicenna in hand and theatrically tossed the hitherto revered and infallible volumes into the roaring flames.

From all reports Paracelsus was a swashbuckling figure with a buccaneer manner and a flair for striking costumes in garish colors along with such appurtenances as clanking swords, yet with a warm and engaging personality that won him many friends. His popularity was further enhanced by his mysterious ability to cure when other doctors failed — a gift that naturally aroused the jealousy and hostility of the conservative physicians, whom he in turn scorned.

His bombast and effrontery became boundless: he claimed to possess a secret product that would prolong life indefinitely; he maintained that he knew everything — and in time convinced even himself of his omniscience.

On one significant occasion when the prominent Canon Cornelius von Lichtenfels was presumed to be mortally ill in the opinion of his doctors, he summoned Paracelsus to his bedside as a last resort — even though he thoroughly loathed the man. When Paracelsus arrived the Canon asked whether he could cure him and what his fee would be, to which Paracelsus replied that he could and would cure him for a stipulated fee, which the Canon considered exorbitant but agreed to. However, after he was duly cured he declined to pay more than half the fee; whereupon Paracelsus sued him but lost his case, because of his own increasing unpopularity and the Canon's political influence and prestige.

The brilliant star that had risen so spectacularly had fallen ignominiously!

Though posterity can never remove the shadow of charlatanry from his image, it does give credit where credit is due and places Paracelsus among the Greats of science.

Treatment of Cardiac Emergencies

DAVID M. CRAIG, M.D.
St. Paul, Minn.

DURING STUDENT days a classmate of mine, working as an externe, was called upon for the first time to pronounce a patient dead. He was a cautious, reserved student and approached this milestone of his career in his usual manner. After careful, methodical, and complete examination he summed up his findings and opinion in a note on the patient's chart: "I was called to see this patient at 6 A.M. He does not respond to oral or painful stimuli. Heart tones and pulse are absent. Breath sounds are absent. Pupils are dilated. No corneal reflexes elicited. The body is cold." He then concluded with the masterly statement: "The patient is apparently dead." At the time it was a remark which caused much amusement; but progress of medicine in the past twenty-five years has been such that we may well wonder when a patient is actually dead.

More deaths today occur from heart disease than from any other single cause. The majority of these deaths must be accepted as the result of inevitable progression of disease until the heart is unable to maintain effective circulation. There are, however, patients in whom the disturbance of heart function is still reversible if treatment is prompt and adequate. The treatment of cardiac emergencies has been adequately covered previously.[1,2] However, the importance of being constantly alert to the possibilities of prompt treatment justifies another review in which I will stress briefly the recognition and management of acute problems which may be encountered in the home, office, or hospital.

Surgical Emergencies

Since the development of modern cardiovascular surgery the prompt diagnosis of rupture or perforation of the heart or great vessels is of paramount importance; for unless it is otherwise contraindicated an attempt at surgical correction is mandatory. The diagnosis of myocardial perforation should be suspected in the patient who develops sudden signs of cardiac tamponade during convalescence from a myocardial infarction or following trauma or penetrating wound of the chest. It can be confirmed by finding gross blood on pericardial puncture. Dissection or beginning rupture of an aortic aneurysm should be suspected when there is severe pain in the back or abdomen, usually radiating downward. Accompanying the pain there is often shock and impaired pulses in the femoral vessels. Further support for the diagnosis will come from X-ray demonstration of widening of the aortic shadow. Degenerative arterial disease is the usual cause of these conditions but the diagnosis should also be suspected when, following trauma, unexplained shock, pain, or vascular enlargement occur. The medical contribution to this emergency is that of prompt diagnosis, evaluation of risk, and arrangement for indicated surgery. Preliminary supportive measures, particularly restoration of blood volume, maintenance of respiration, relief of pericardial tamponade, may sustain a patient long enough for successful surgery to be accomplished.

Cardiac Tamponade

Cardiac tamponade should be suspected when there is increasing dyspnea, venous pressure and heart size, a fall in pulse pressure, decreased heart sounds, and paradoxial pulse. This may occur because of an effusion complicating an acute pericarditis or rheumatic heart disease, or from hemopericardium associated with myocardial infarction or trauma. When the symptoms are severe and appear to be life-threatening, prompt relief may be obtained by pericardial aspiration by the subxiphoid or apical approach. If fluid recurs, or if hemopericardium is due to injury or rupture of the heart, surgery may be required.

Ventricular Standstill or Fibrillation

The most urgent cardiac emergency is created by cessation of heart action by ventricular standstill or fibrillation. Usually this is the inevitable termination of progressive heart disease. There are, however, patients previously healthy in whom cardiac standstill occurs in hearts still capable of efficient function. This is especially true in cases of electric shock, asphyxia, or standstill occurring during anesthesia or in acute myocardial infarction. The introduction of closed-chest cardiac compression following the work of Kouwenhoven and Jude[3] has permitted many lives to be saved without resort to thoracotomy with its attendant technical difficulty and risks.

The chart (Fig. 1) developed by the Council of Cardiovascular Surgery of the American Heart Association summarizes the essential points of technique which should be familiar to every physician.

It should be emphasized that if standstill is suspected, oxygenization of the body tissues through artificial respiration and circulation must be started immediately by those present without waiting for further confirmation or arrival of special equipment or personnel. If the resuscitator is alone, he should begin with three or four lung insufflations which are repeated after each thirty seconds of cardiac compression until help arrives. After restoration of the heartbeat the patient must be observed carefully to assure continued adequacy of circulation.

Cardiac standstill of short duration occurs as Stokes-Adam syndrome in patients with atrio-ventricular block. These attacks usually terminate spontaneously; but, if frequent, are disabling and may cause cerebral damage from repeated ischemic episodes. Diagnosis is suggested by a typical history of syncopal attacks in a patient with heart block. It is confirmed by the electrocardiographic record of an attack. Exact diagnosis is important because occasionally similar clinical manifestations may result from paroxysms of ventricular tachycardia.

Treatment

The treatment is concerned, first, with the restoration of the heartbeat and second, with the establishment of an adequate cardiac pacemaker so as to prevent further attacks. With the onset of cardiac standstill the following are indicated:

Restoration of Heart Beat

(1) A sharp slap on the chest which may initiate heartbeat;

(2) External cardiac massage to maintain circulation;

(3) Epinephrine (1:1000) 0.2-0.5 cc. given intravenously;

(4) If the heartbeat is not restored, the management is that of cardiac standstill.

Maintenance of Pacemaker

If the heartbeat is restored it is necessary to maintain a cardiac pacemaker for prevention of further episodes of standstill:

(1) Isuprel 10-15 mgm. sublingually, repeated as frequently as every fifteen minutes if needed to maintain a suitable heart rate;

(2) Ephedrine Sulfate 25-50 mgm. orally every three to six hours;

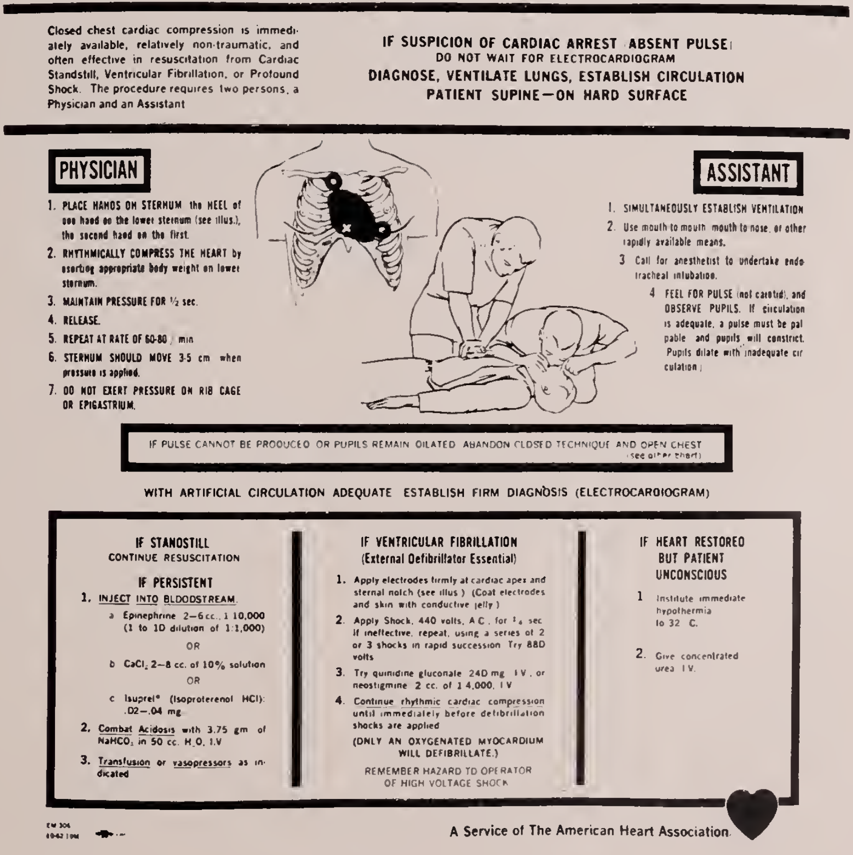
(3) If the above are not controlling episodes, intravenous administration of Isuprel or Epinephrine in dosage of 4 mgm. in a liter of dextrose administered at a rate sufficient to keep the pulse between 30 and 45 beats a minute. If this is controlling the attacks, dosage can be gradually reduced and the patient switched to oral therapy;

(4) Kaliuretics (chloralthiazide or one of the derivatives from it) may be given in sufficient doses to depress the serum potassium concentration and increase the excitability of the ectopic ventricular pacemaker.

(5) Implantation of electrodes for electronic pacemaker. Where medicinal means have failed, this will frequently permit a patient to carry on with normal activity and freedom from attacks.

Arrhythmias

Other cardiac arrhythmias may require emergency treatment when, occurring in the presence of underlying disease, they compromise cardiac function. Thus, for example, tachycardia in the normal heart may usually be tolerated for long periods, but in the presence of disease the shortening of the diastole by the rapid rate may dangerously decrease cardiac and coronary flow. There are also times when the extreme anxiety precipitated by the arrhythmia may create an emergency situation. For definite diagnosis of an arrhythmia an electrocardiographic record is usually necessary. In an emergency situation an astute clinician should be able to make the correct diagnosis with a high degree of accuracy from the clinical findings.



Closed chest cardiac compression is immediately available, relatively non-traumatic, and often effective in resuscitation from Cardiac Standstill, Ventricular Fibrillation, or Profound Shock. The procedure requires two persons, a Physician and an Assistant

IF SUSPICION OF CARDIAC ARREST (ABSENT PULSE)
DO NOT WAIT FOR ELECTROCARDIOGRAM
DIAGNOSE, VENTILATE LUNGS, ESTABLISH CIRCULATION
PATIENT SUPINE—ON HARD SURFACE

PHYSICIAN

1. PLACE HANDS ON STERNUM the HEEL of one hand on the lower sternum (see illus.), the second hand on the first.
2. RHYTHMICALLY COMPRESS THE HEART by exerting appropriate body weight on lower sternum.
3. MAINTAIN PRESSURE FOR ½ sec.
4. RELEASE.
5. REPEAT AT RATE OF 60-80 / min
6. STERNUM SHOULD MOVE 3-5 cm when pressure is applied.
7. DO NOT EXERT PRESSURE ON RIB CAGE OR EPIGASTRIUM.

ASSISTANT

1. SIMULTANEOUSLY ESTABLISH VENTILATION
2. Use mouth to mouth, mouth to nose, or other rapidly available means.
3. Call for anesthetist to undertake endotracheal intubation.
4. FEEL FOR PULSE (not carotid), and OBSERVE PUPILS. If circulation is adequate, a pulse must be palpable and pupils will constrict. Pupils dilate with inadequate circulation.)

IF PULSE CANNOT BE PRODUCED OR PUPILS REMAIN DILATED ABANDON CLOSED TECHNIQUE AND OPEN CHEST (see other chart)

WITH ARTIFICIAL CIRCULATION ADEQUATE ESTABLISH FIRM DIAGNOSIS (ELECTROCARDIOGRAM)

IF STANDSTILL
CONTINUE RESUSCITATION

IF PERSISTENT

1. INJECT INTO BLOODSTREAM.
   - a Epinephrine 2–6 cc., 1:10,000 (1 to 10 dilution of 1:1,000)
     OR
   - b $CaCl_2$ 2–8 cc. of 10% solution
     OR
   - c Isuprel® (Isoproterenol HCl): .02–.04 mg
2. Combat Acidosis with 3.75 gm of $NaHCO_3$ in 50 cc. H_2O, I.V.
3. Transfusion or vasopressors as indicated

IF VENTRICULAR FIBRILLATION
(External Defibrillator Essential)

1. Apply electrodes firmly at cardiac apex and sternal notch (see illus.) (Coat electrodes and skin with conductive jelly.)
2. Apply Shock, 440 volts, A.C., for ¼ sec. If ineffective, repeat, using a series of 2 or 3 shocks in rapid succession. Try 880 volts
3. Try quinidine gluconate 240 mg. I.V., or neostigmine 2 cc. of 1:4,000, I.V.
4. Continue rhythmic cardiac compression until immediately before defibrillation shocks are applied

(ONLY AN OXYGENATED MYOCARDIUM WILL DEFIBRILLATE.)

REMEMBER HAZARD TO OPERATOR OF HIGH VOLTAGE SHOCK

IF HEART RESTORED BUT PATIENT UNCONSCIOUS

1. Institute immediate hypothermia to 32° C.
2. Give concentrated urea I.V.

EM 304
10-62 10M

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Atrial Fibrillation

Diagnostic Clues

Rapid, grossly irregular rate, particularly by premature beats without a following compensatory pause.

Treament

Digitalization till ventricular rate 70-90. Then may attempt restoration of sinus rhythm with Quinidine.

Atrial Flutter

Diagnostic Clues

Absolutely regular rate 140-180 unless there is shifting rather than 2:1 block. Changes with exercise or vagal stimulation are stepwise, rather than gradual.

Treatment

Digitalization till ventricular rate slowed; sinus rhythm restored; or atrial fibrillation occurs.

Atrial Tachycardia

Diagnostic Clues

Absolutely regular rate of 160 or faster. Vagal stimulation has no effect or may abruptly terminate attack. Usually occurs in young persons without heart disease.

Treatment

Vagal stimulation (Valsalva maneuver, carotid sinus pressure — singly and together.); digitalization followed by vagal stimulation; sedation (Morphine 10-15 mgm.); Quinidine.

Atrial Tachycardia with Block

Diagnostic Clues

Usually occurs in patient under treatment for heart disease frequently due to digitalis toxicity. Rate variable depending on block.

TABLE I

Minimal Contents of a Cardiac Emergency Kit

1. 4 2 cc. syringes with needles #23-25 (Disposable plastic syringes are most convenient).
2. 3 rubber tourniquets (to restrict venous return).
3. Medications —

Drug	Dose	Available in	Notes
Morphine sulfate or Meparidine	7.5-15 mgm. (IV) 50-100 mgm. (IV)	15 mgm./cc. vials 50 mgm./cc. vials	For congestive failure — coronary thrombosis. Use Cautiously and in smaller doses in older persons. — Repeat as needed.
Aminophyllin	0.25-0.5 gm. (IV)	2 cc. ampoules 10 and 20 cc. ampoules	For congestive failure. If given slowely over at least 10 minutes the 2 cc. ampoules may be used (IV). Administration should be stopped if nausea, dizziness, palpitation or hypotension occur.
Epinephrine	0.2-0.5 cc. (H) or (IM) 1/1000 solution	1 cc. ampoules	For cardiac standstill or Stokes-Adams. Should be used IV or intracardiac. To maintain pacemaker may give by IV drip 4 mgm. in 1000 cc. 5% dextrose solution.
Pronestyl	100 mgm./min. (IV) for 5-10 minutes	100 mgm./cc.-10 cc. vial	For ventricular tachycardia. Patient should be watched closely for change of rhythm or hypotension.
Vasopressor (Aramine)	2-10 mgm. (IM)	10 mgm./cc. 1 cc. ampoule 10 cc. vial	For heart block. Repeat as needed, or add 100 mgm. to 1000 cc. IV solution; regulate flow to maintain pressure.
Quindine Sulfate	1-2 tablets Q hr. for 5 doses	0.2 gm. tablets	For arrhythmia. To prevent arrhythmia use .200-.400 TID.
Digitalis (Lanoxin-IV)	(IV) 1 mgm. then 0-25 mgm. (IV) Q 2 hrs.	2 cc. ampoules (1 mgm.)	For heart failure or arrhythmia. Use cautiously if previous digitalis; repeat doses till therapeutic result or toxicity is reached.
Lanoxin (oral)	1-3 mgms. then 0.25-0.5 mgms.	0.25 and 0.5 mgm. tablets	
Isuprel	15 mgm. q 1-3 hrs. sub lingually	10-15 mgm. sub lingual tablets	To increase cardiac rate in heart block. Does not raise blood pressure.

Treatment

Stop digitalis until normal rhythm restored. Potassium chloride 1 to 2 gms. q 4 hrs. orally or 20 to 40 millequivalents in 500 cc 5% dextrose in water intravenously. Check frequently with electrocardiogram to note correction of rhythm or signs of hyperkalemia. If not due to digitalis toxicity treat as atrial flutter.

Ventricular Tachycardia

Diagnostic Clues

Usually a complication of myocardial infarction or digitalis toxicity. No history of previous attacks. Rate 160-210 with slight irregularity of rhythm and heart tones because of independent atrial contractions. No effect from Vagal stimulation.

Treatment

Pronestyl (100 mgm. IV q two to five minutes to maximum dose of 1 gm. Vasopressors to control hypotension. Patient must be watched closely for change in rhythm or hypotension (preferably monitored by electrocardiogram. If the patient is not critical, may use oral medication (Pronestyl 250-500 mgm. q two hours, Quinidine 400 mgm. q hrs. for five doses).

The Use of Electric Shock

Recently the use of a timed direct-current electric shock to stop arrhythmias has been introduced by Lown.[4] When this technique is utilized the conversion is instantaneous. The myocardium is not rendered toxic by medication and many cases have reverted which did not respond to medical regimes. If the present promise of the "cardioverter" persists, this may well replace many of the methods now used to control arrhythmias.

Left Ventricular Failure

Left ventricular failure is probably the most commonly encountered cardiac emergency. It occurs primarily in hypertension, aortic disease, and myocardial infarction. Regardless of the etiology, left ventricular failure is characterized by a relative fall in left ventricular output, pulmonary congestion, and symptoms of acute dyspnea, cough and orthopnea. Diagnosis is based on these symptoms with findings of rales throughout the lungs, often wheezing respirations, and in severe cases, constant cough with production of frothy, frequently bloody, sputum.

Treatment

Treatment to correct the abnormal physiology and return cardiac function toward normal should be started promptly and continued intensively until symptoms are relieved.

1. Sitting position in bed or comfortable chair.
2. Tourniquets producing venous congestion of three extremities — rotating every ten minutes.
3. Morphine sulfate 10-15 mgm. IV or meparaidine 50-100 mgm. IV. (This gives the quickest relief by relaxing the patient, easing work of respiration and cough; *it should be repeated as needed).*
4. Intravenous digitalis — if not digitalized.
5. Aminophyllin 0.25-0.5 IV (given *slowly* over five minutes).
6. Mercurial diuretic IM or IV (may be mixed with the aminophyllin).
7. Oxygen by mask or nasal catheter. Bubbling the oxygen through 95% ethyl alcohol adds to the defrothing action.
8. Positive pressure breathing.
9. Venesection of 500-1000 cc.
10. Personal attention and reassurance given by a competent physician. This last item is included because left heart failure is a rapidly changing condition. No set formula can be followed and the physician must be ready to modify treatment as dictated by direct clinical observation.

Summary

This review has presented briefly some of the important cardiac emergencies encountered in practice. It is obviously incomplete, and certain entities such as myocardial infarction have not been considered specifically. Rather, the individual complications of the myocardial infarction should be considered as emergency problems. Because of the need for quick action when confronted with a cardiac emergency a special kit is of value, which should have the necessary drugs and equipment available for immediate use. It should be small enough to occupy a place in the physician's bag or be easily carried separately. There are many types of medication available, but each physician should use those he is familiar with. In the preceding tabulation I have listed the equipment which I feel is essential and those medications that I ordinarily use:

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3. Kouwenhoven, W. D., Jude, J. R. and Knickerbocker, G. G.: Closed-chest Cardiac Massage. JAMA 181:127, 1962.
4. Lown, B., Amorasingham, R., and Neuman, J.: New Method for Terminating Cardiac Arrhythmias. JAMA 182:548, 1962.

From Bulrushes to Tularemia

The disease tularemia acquired its name by an interesting series of steps.

During the Mexican ownership of California the areas where a species of bulrushes, tule (Spanish tollen), grew abundantly were called tulares. Subsequently, a California county was appropriately named Tulare County.

About 1906, after the San Francisco earthquake and fire, an epidemic disease smote the ground squirrels in the tule area. Because of its resemblance to bubonic plague, health authorities were alerted and investigation begun. When the elusive microorganism causing the disease was finally isolated, the Public Health Service happened to be concentrating their research in Tulare County; hence the name bacterium tularense for the newly identified culprit.

When later a few baffling cases of similar infection in man reached the attention of the authorities, detection efforts were accelerated and the mystery solved when Dr. Francis' investigations established that the human infection under scrutiny was due to bacterium tularense entering man's blood via the stings of flies or ticks infected earlier by biting sick ground squirrels.

Hence the name tularemia — combining tularense (the bacterium) with emia (blood).

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Description: Each scored tablet contains 5 mg. ‘Methedrine’ brand Methamphetamine Hydrochloride.

Dosage: 2.5 mg. (½ tablet) 3 times daily. May be increased gradually according to response; more than 10 mg. daily rarely is needed. The last dose of the day should not be taken later than 6 hours before bedtime.

Side effects: Insomnia may occur if taken later than 6 hours before retiring. The usual peripheral actions of sympathomimetic amines (vasoconstriction and acceleration of the heart) are minimal and little noticed on low or moderate dosage.

Contraindications and precautions: Should not be used in patients with myocardial degeneration, coronary disease, marked hypertension, hyperthyroidism, insomnia or a sensitivity to ephedrine-like drugs. Moderate hypertension in the obese is not necessarily a contraindication since it may be relieved as the overweight is reduced.

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Editorials

Peripheral Arterial Embolization and Thrombosis

THE FIRST successful embolectomy was performed by Labey in nineteen hundred and eleven. Warren has described three phases in time through which the procedure of embolectomy has passed.* The first phase extended to nineteen hundred and thirty five and consisted of isolated instances of embolectomy with the rare salvage of limb and life. The second phase extended from nineteen hundred and thirty five to nineteen hundred and fifty. During this period the medical profession learned that early operative treatment bore fruit and limb salvage was increased to eighty-five per cent. Aortic embolectomy was performed successfully. The third phase was entered in nineteen hundred and fifty. At that time surgeons, especially those concerned with the mitral stenosis, became acutely aware of the problem of peripheral arterial emboli and treated the embolus aggressively.

Most peripheral arterial emboli originate in the left side of the heart. Warren's review showed that forty-eight per cent of arterial emboli originated in patients with rheumatic heart disease associated with auricular fibrillation and mitral stenosis. An additional twenty-one per cent occurred in patients with rheumatic heart disease and mitral stenosis but without auricular fibrillation. A second common cause is a myocardial infarction and the mural thrombus. This accounts for about fifteen per cent of emboli. Additional sources are arteriosclerotic changes in the wall of the aorta and peripheral arterial aneurysms. On one occasion I have seen the diagnosis of myxoma of the left atrium made following an abdominal aortic embolectomy in a patient who had "mitral stenosis."

The symptoms of acute arterial occlusion consist of pain and the loss of function. The pain is usually constricting in type and severe. However, it may be surprising how slight the pain may be in a particular patient. The loss of function is both sensory and motor. Loss of sensation and paralysis of the small muscles of the feet or hands is common. The pulse will be exaggerated just proximal to the embolus. Oscillometric examination may also be useful in determining the specific level of the lodgement of the embolus.

The natural course of the disease following embolization depends upon the effectiveness of the collateral arterial blood supply, the duration and extent of the reflex arterial spasm, the development of progressive thrombosis not only distal but also proximal

Continued

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*ARCH Surgery 85:905, 1962.

most effective in the obese diabetic...

Recent reports suggest...insulin and sulfonylureas may accelerate lipogenesis,[1-5]...serum "insulin" levels are often elevated in obese diabetics[2,3,6]... DBI (phenformin HCl) reduces high blood sugars, lowers elevated "insulin" levels, tends to reduce body weight toward normal.[1,3,7-9]

In the obese diabetic (ketoacidosis-resistant), use of phenformin HCl together with a proper diet: **A.** acts to reduce high blood sugar without increasing fat synthesis or weight gain. **B.** does not increase already elevated endogenous insulin levels; may, indeed, act to restore more normal insulin levels. **C.** favors reduction of weight towards normal.

In the ketoacidosis-resistant obese diabetic not amenable to diet alone, hypoglycemic phenformin HCl appears to help avoid weight gain or reduce adiposity, factors which otherwise tend to make blood sugar control more difficult and to increase the likelihood of complications. However, in the ketoacidosis-prone diabetic, insulin is still the essential hypoglycemic agent.

Summary: Indicated in stable adult diabetes, sulfonylurea failures and unstable diabetes. Gastrointestinal side effects occurring more often at higher dosage levels abate promptly upon dosage reduction or temporary withdrawal. Occasionally an insulin-dependent patient will show "starvation" ketosis (acetonuria without hyperglycemia) which must be differentiated from "insulin-lack" ketosis, and treated accordingly. Use with caution in severe liver disease. Not recommended without insulin in acute complications (acidosis, coma, infections, gangrene, surgery). Consult product brochure for full information.

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to the embolus and finally upon the anatomic location of the embolus. If the above factors all act conjointly to decrease the effective collateral arterial supply, the extremity may become mortified in eight hours. At the other end of the spectrum the symptoms may begin to abate in minutes with recovery and no loss of tissue. In Warren's series the locations were as follows: internal carotid and its branches — twenty-five per cent, aorta — eighteen per cent, the femoral artery — thirty-one per cent, and the popliteal artery — six per cent.

Treatment of embolization is directed to removal of the occlusion surgically whenever possible. While the operating room is being prepared, two damaging complications can be treated. The arterial spasm is best treated by injecting procaine into the sympathetic ganglia which supplies the area involved. The tendency of the intraluminal clot to extend as a distal thrombosis can then be treated by anticoagulating the patient by the use of intravenous heparin. This should then be followed by surgical removal of the embolus. Due to the primary myocardial pathology in most of these patients, the operation is usually performed under local anesthesia. When the embolism involves only small arteries, sympathetic block followed by anticoagulation may be sufficient to prevent loss of tissue or symptoms of arterial insufficiency after recovery. When larger vessels are involved such treatment may prevent tissue loss but doom the patient to symptoms of chronic arterial insufficiency. The embolectomy should be done as an emergency allowing as little lapse of time as possible. A few hours may make the difference between life or mortification of a limb. A specific rule can not be made concerning the time interval following which surgery is still possible. The only limiting factor is the viability of the limb. In the leg nonviability is evidenced by rigidity in the anterior muscle compartment. Embolectomy should be performed within eight hours; however, many limbs have been saved after forty-eight to ninety-six hours. After ninety-six hours one must be aware of the diagnosis of myoglobinuria following reconstruction of the arterial blood flow and be willing to amputate the leg if tubular necrosis occurs.

Embolism of the aortic bifurcation represents the most urgent surgical problem. The mortality of nonsurgical treatment approaches ninety per cent. The mortality rates quoted from most centers vary between thirty-two and thirty-eight per cent. The salvage or survival rates for extremities treated by embolectomy is eighty-five to ninety per cent. The mortality rate is surely a reflection of the primary cardiac pathology.

By far the best results obtained following embolectomy are those operated prior to the occurrence of distal thrombosis. If circumstances preclude doing the embolectomy before distal thrombosis occurs, one must try to remove the distal thrombus as well as the embolus. The success or failure of the thrombectomy will depend upon the degree of adherence between the thrombus and the arterial wall.

John C. Parrott, M.D.
Minneapolis, Minn.

A Critical Look at Our Approach to Causation of Disease

MEDICINE HAS many important goals, among them the prevention and cure of disease, the alleviation of suffering, the saving of life, and finally the improvement of the efficiency and happiness of mankind. Hence a vital objective is the determination of the causation of disease. This end is paramount, for without it we cannot know how to treat, control, or cure disease.

In some cases successful measures are empirically possible without precise

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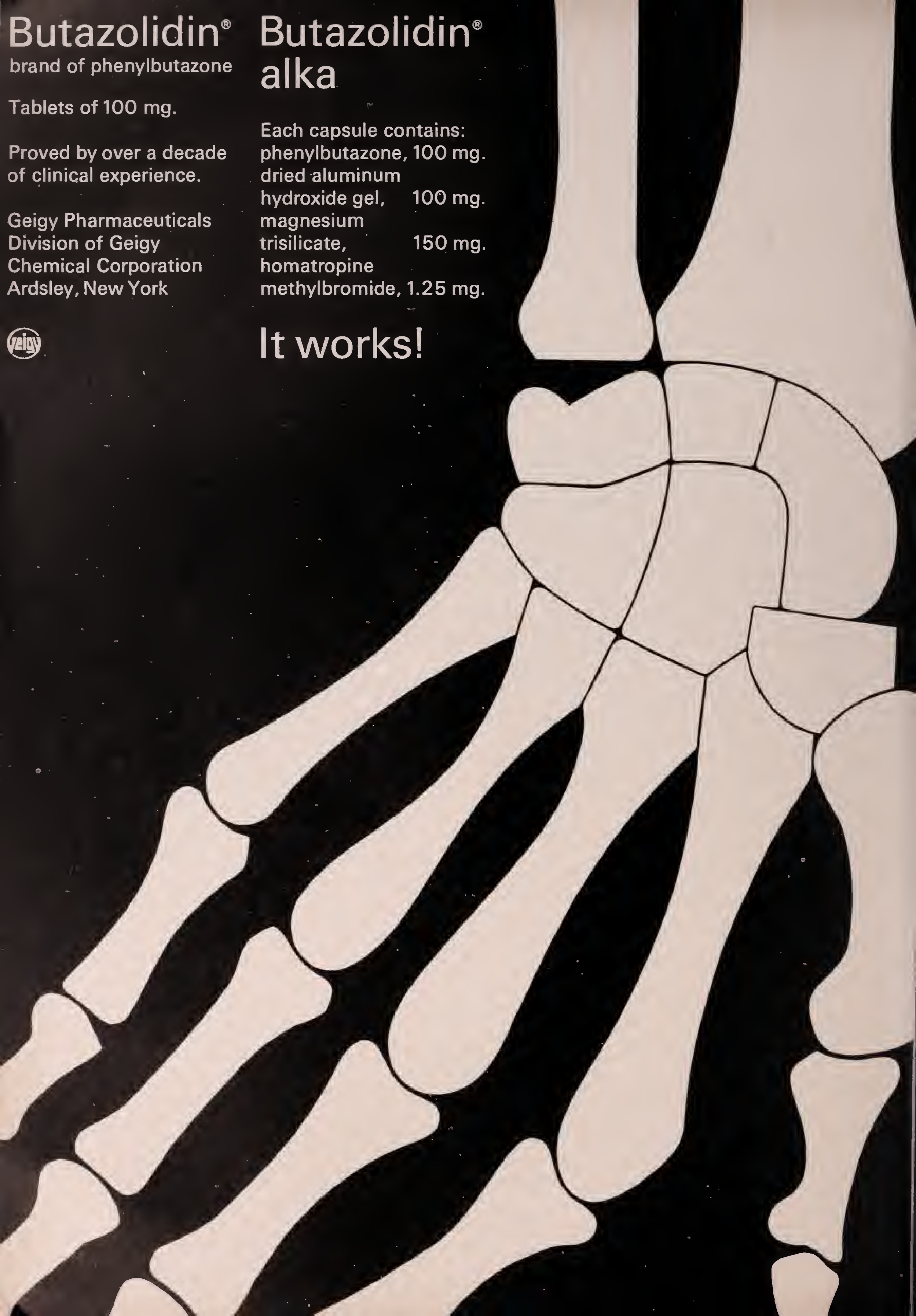

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knowledge of causes; but these instances are notable solely because they are exceptions. Our long-range medical successes depend upon knowing the exact causes of given diseases. We search diligently and persistently; but sometimes in our all too human efforts we proceed blindly and are unconsciously conditioned by emotion and bias.

Before developing this theme, however, a moment's review is in order. We physicians today rightly pride ourselves on remarkable advances, many of which are relatively recent; in fact some of the most dramatic medical breakthroughs have occurred within the life span of those here today. The progress in surgery, the advent of antibiotics, the application of medical electronics, the Salk vaccine, and many other advances come to mind. However, in assessing modern medical progress we should not neglect the lessons of the past, for these milestones convey a message for us today.

What are these signposts and what do they tell us?

In Egypt over 4,000 years ago healings were effected by invocations to the gods.

Over 1,000 years before Christianity Moses drew up for the Hebrews a rational sanitary code, the rules of which were incorporated into the Jewish religion, with observance enforced by the priests.

Before the time of Hippocrates, acknowledged as the man who gave us the beginning of scientific medicine, the Greeks believed that the gods dispensed disease and that only the gods could cure.

During the great plagues which periodically swept Europe during the Middle Ages the conviction prevailed that these scourges were divine retribution for the evils of mankind.

In the late seventeenth century during the notorious Salem witchcraft trials, many of the victims of the infamous persecution were undoubtedly either mentally ill or merely senile; yet they were regarded as possessed by the devil, and the Biblical injunction "Suffer not a witch to live" was interpreted literally and applied barbarously in the case of many a harmless and innocent but perhaps unconventional and unorthodox member of the social group.

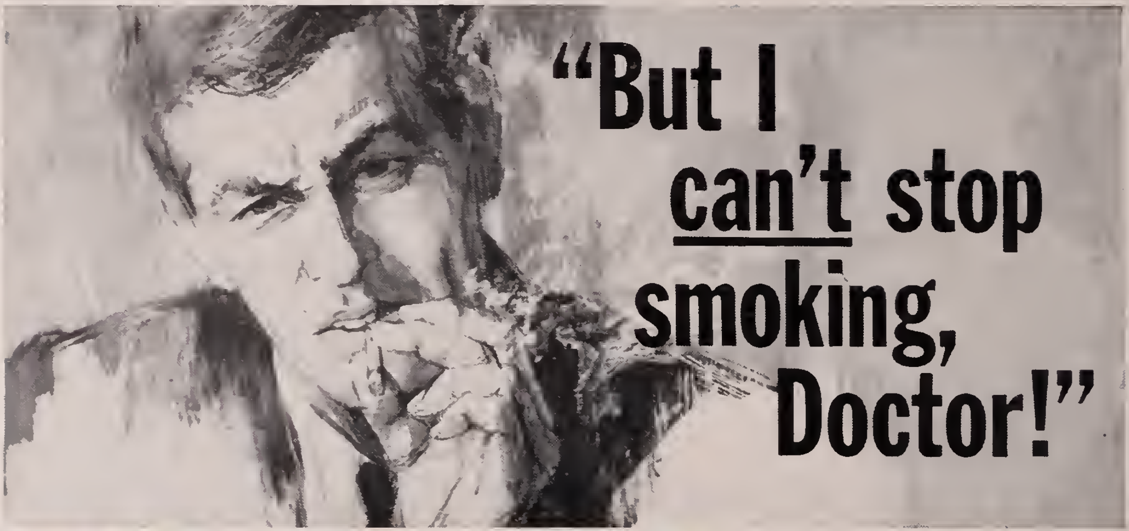
From these random signposts it is evident that throughout mankind's checkered and chaotic career the twin strains of religion and medicine have been inextricably interwoven. Even though the strands seem to have been disentangled in the more cultured and sophisticated societies, there still remains a residual legacy of superstition, mysticism, and fear, which permeates and affects our thinking and behavior.

The scriptural utterance "For the wages of sin is death" still tolls with awesome finality across the centuries; and no matter how scientifically secure we may feel in our recently acquired knowledge, this dread decree still lurks deep in our unconscious to haunt us with its sinister echoes when we are off guard. Who has not heard the victim of a sudden accident or an unexpected disease ask ruefully: "Why did this happen to me?", and someone reply half in jest and half in earnest: "You must have been a bad boy (girl)."

We may smile indulgently if not superciliously at the idea that supernatural forces have something to do with the causation of disease; but this ancient delusion persists even today to shadow and distort our judgment; in America and especially in less civilized countries medicine men, sachems, peyote wizards, witch doctors, and countless other frauds and fakes cast unholy spells, chant weird incantations, and mix horrendous brews to ward off and to cure all ills flesh is heir to.

Continued

When your patient says: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- Encourage patient cooperation through pleasant taste.

Dosage and Administration: In order to obtain the maximum benefit, a NIKOBAN Pastille should be sucked slowly and taken according to the schedule below. Whenever possible a pastille should be taken after meals.

1st week: 1 pastille every 1 to 2 hours for a maximum of 12 pastilles daily. *2nd week:* 1 pastille every 3 hours. *3rd week:* 1 pastille every 4 hours. *4th week:* 1 pastille every 4 to 6 hours. *Thereafter* 1 pastille may be taken at infrequent intervals whenever necessary. In some instances there may at first be a slight astringent burr of the tongue and throat. This will usually disappear as treatment with NIKOBAN Pastilles progresses and is no cause for concern.

Caution: It is advisable neither to smoke nor to use a smoking deterrent during pregnancy.

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References: 1. Goodman, L. S. and Gilman, A.: The Pharmacological Basis of Therapeutics, New York, Macmillan, 1960, Ed. 2, pp. 620-622; 2. Edmunds, C. W.: J. Pharmacol. and Exper. Therap., 1:27, 1909; 3. Hazard, R. and Savini, E. Gand., 92:471, 1963. 4. Dorsey, J. L.: Ann. Int. Med., 10:628, 1936; 5. Rasmussen, K. B.: Ugeskr.laeger, 118:222, 1956; 6. Ejrup, B.: Sven. lak. Tid., 53:2634, 1956; 7. Jochum, K. and Jost, F.: Munch. med. Wchnschr., 103:618, 1961; 8. Jost, F. and Jochum, K.: Med. Klin., 54:1049, 1959; 9. Smoking and Health, Summary and Report of the Royal College of Physicians of London on Smoking. New York, Pitman, 1962.

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We have recently emerged from a progressive period in which bacteriological causes of disease have been fairly well established; and we have already entered a new era where viral causation is being explored. Beyond the bacterium and the virus, however, we are faced with a multitude of diseases that baffle us: leukemia, cancer, Hodgkin's disease, arteriosclerosis, etc. In our laudable but impatient desire, however, to ascertain the causes of these elusive diseases, we are frequently over-enthusiastic in grasping at straws and blindly accepting premises we have neither the moral courage nor the intellectual integrity to substantiate for ourselves.

Futhermore we are faced today with an entirely new approach: the statistical and epidemiological — with which most of us are not familiar, since its application is neither simple nor exact. Our past training has been on the sound principle of Koch's postulates; most of us are not statistical experts and have neither the time, the talent, nor the temerity to question the premises of those statisticians who propose new and revolutionary theories for the causation of disease.

Many of the statistical approaches today are not necessarily valid and may lead to incorrect and improper conclusions. I am certain from my own critical observations that the statistician's approach to a problem has often been influenced by his private convictions and personal beliefs. For example, the individual who smokes has difficulty in determining "statistically" that smoking is harmful; while the nonsmoker has no trouble "proving" that tobacco causes disease. Likewise the individual who indulges in alcohol can find no figures to indicate that it produces disease; whereas the abstainer finds alcohol the root of all evil. The theory that overweight and a high cholesterol level cause arteriosclerosis has its proponents pro and con, statistically speaking.

Now it appears that such approaches to the causation of disease all revolve about pleasurable activities: overindulgence in tobacco, alcohol, rich food. On the other hand, maintaining a high moral standard, avoiding pleasure, and living ascetically are apparently never indicted as causes of disease. Only that behavior which is guiltily pleasurable and therefore, in a religious sense, sinful, brings retribution.

Unfortunately, in our unfamiliarity with the new statistical methods and in our haste to conquer those diseases that have so far eluded the purely scientific approach, we have unconsciously but unjustifiably permitted ourselves to jump to unwarrantable conclusions, supported and colored by our social mores and culture and by our own personal predilections. As yet we have not learned to screen out irrelevant, insidious influences; our private prejudices endure and the ghosts of our early religious indoctrination and of the tribal superstitions of our ancestors still walk and beckon us astray.

To further illustrate my contention that statistics can be used to "prove" a point I am inserting here a prime example that recently came to my attention. The Minneapolis Sunday Tribune of February 3, 1963, reported that a statistical survey by the Russians now shows that baptism causes heart disease; and as further proof of this, the statistic is given that during the Christian era in Russia the average length of life was 32 years, whereas now it is 69 years: startling proof to the Russians that Christianity was a cause of shortened life expectancy.

In further substantiation of my general thesis I quote here in part from Oliver Wendell Holmes' "Currents and Counter-Currents":

"First there is the natural incapacity for sound observation which is like a faulty ear in music. We see this in many persons who know a good deal about

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books, but who are not sharp-sighted enough to buy a horse or deal with human diseases.

"Secondly, there is in some persons a singular inability to weigh the value of testimony.

"The inveterate logical errors to which physicians have always been subject are chiefly these:

"The mode of inference PER ENUMERATIONEM SIMPLICEM, in scholastic phrase; that is, counting only their favorable cases. This is an old trick illustrated in Lord Bacon's story of the gifts of the shipwrecked people hung up in the temple. Behold! they vowed these gifts to the altar, and the gods saved them. Ay, said a doubting bystander, but how many vows of gifts and were shipwrecked notwithstanding? The numerical system is the best corrective of this and similar errors.

"The POST HOC ERGO PROPTER HOC error: he got well after taking my medicine; therefore in consequence of taking it.

"The false induction from genuine facts of observation, leading to the construction of theories which are then deductively applied in the face of the results of direct observation.

"And lastly, the error which Sir Thomas Browne calls giving 'a reason of the golden tooth'; that is assuming a falsehood as a fact, and giving reasons for it, commonly fanciful ones, as is constantly done by that class of incompetent observers who find their 'gold tooth' in the fabulous effects of the homeopathic materia medica, — which consists of milk and a nomenclature."

Finally, these observations of mine do not constitute a plea to stifle new approaches, but rather to take a long, hard look at them to avoid making errors in their application, thus causing more harm than good. One of the partial prices for progress each generation must pay is thorough and conclusive testing and confirming of new theories in the light of current knowledge. This does not however give us as physicians the license to deprive the present generation of the right to live, rather than to exist.

Arthur Kerkhof, M.D.
Minneapolis, Minn.

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*Presented at Mediclinics, Ft. Lauderdale, Florida, March, 1963.

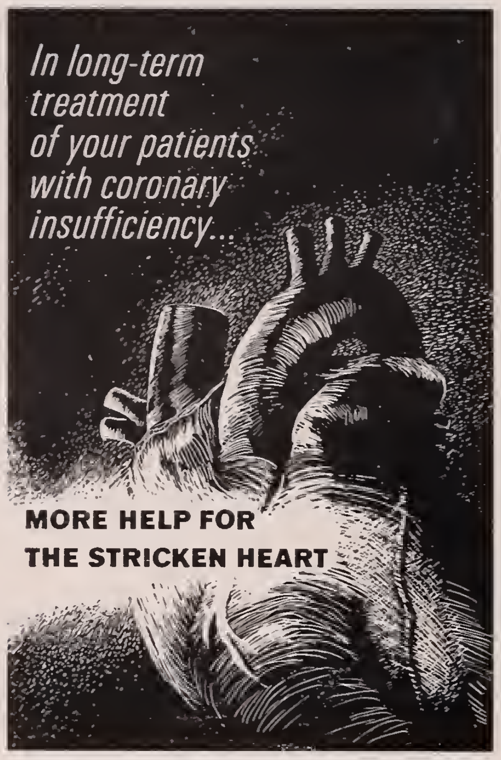
Letter to the Editor:

Editor's Note: The following is an excerpt from a letter concerning an editorial in the February 1964 issue of MINNESOTA MEDICINE. Dr. Pruitt was challenged on the usage of "referee" as one who writes a letter of reference:

To the Editor:

You may be sure that I struggled over the matter of what to call one who writes a letter of reference. Webster defines a referee as, "one to whom a thing is referred." Supported by this generously loose definition and by my own concept that one who writes a letter of reference serves, in a sense, as an arbitrator between the candidate for appointment and the

Continued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institution with an appointment that needs to be filled, I concluded the word "referee" was reasonably appropriate and more appropriate than any other I could track down.

Raymond D. Pruitt, M.D.
Dept. of Internal Medicine
Baylor University
Houston, Texas

Presidents Letter continued from Page 247

held in the Mayo Auditorium.

There is no need to go into details of the administration of the plan here but I would like to mention some of the agreed-upon, desirable qualifications of the nominees for the Awards: extraordinary knowledge of the subject; clarity of presentation; skillful technique; ability to stimulate the pursuit of greater knowledge; devotion to high standards of medical care; concern for the student's comprehension of material and for his welfare.

Your Council approved the plan and made the necessary appropriation for this year. It seems that this is a fine chance for practicing physicians, through their State Medical Association, to recognize excellence in a highly important field, and also to participate under favorable circumstances in the graduation ceremonies of the Medical School.

J. P. Medelman M.D.

J. P. Medelman, M.D.
President
Minnesota State Medical Association

Photographic Contest

The Doctor's Photographic contest continues each month. Send in your entries to the Photo Contest Editor, MINNESOTA MEDICINE, in accordance with the rules page 34 of the January issue. The winning photograph each month will be printed on the cover of a subsequent issue of MINNESOTA MEDICINE.

Aphasia

Isn't it peculiar that the human brain begins to function from the moment you are born, improves as you grow older, then stops completely when you stand up to talk?—News-Leader, Arcadia, Wis.

A shriek in the dark has its own value, its own beauty.—Peter Ustinov

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Curbstone Consultation

Bee Stings

QUESTION: What is the nature of the venom of the bee producing the poisonous reaction and what is the recommended immunization program against bee stings?

M.D., New Ulm

ANSWER: The bee belongs to the Hymenoptera group of arthropods. The Hymenoptera group include the honeybee, bumblebee, wasp, yellow and black hornets, and yellow jacket. It is said that the venom of these stinging insects is just as potent and causes more deaths in the United States than the venom from the bite of a rattlesnake. The nature of the venom consists of complex chemical substances which produce marked local irritative reactions and protein fractions producing allergic responses. Chemicals identified in the venom include indol derivatives, choline, glycerol, phosphoric acid, palmitic and other fatty acids, and a non-nitrogenous substance thought to be saponin. It may be that this latter material causes a release of histamine from the skin through the interaction of dermolysin. Perhaps the sensitization following the sting by a bee is caused by proteins inherent in both the body and secretions found in the venom sac. Persons who have been stung and experience mild to moderate reactions only may not need desensitization. However, those who have experienced severe local or generalized allergic reactions from previous stings should probably receive desensitization therapy with polyvalent insect whole body extracts. Sudden death from anaphylaxis can result to individuals who are once sensitized to the protein substances of stinging insects when they are restung. Desensitization with the polyvalent extracts is believed to be about 95% effective in protecting against anaphylactic reactions.

You can't keep trouble from coming, but you needn't give it a chair to sit in.

—Henry Martin

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Tumor Conference

Lymphosarcoma Involving the Stomach

Lymphosarcoma of the stomach is relatively uncommon, comprising about three percent of all gastric tumors. There is no typical clinical picture.

The disease may start with a history of anorexia. Recent or changing dyspeptic symptoms, progressive loss of weight and roentgenologic findings suggestive of carcinoma of the stomach may be present. Studies of free acid reveal a normal distribution of acid values. Benzidine tests of the feces usually do not show occult blood. Gastroscopy may show hyperrugation of the involved and/or adjacent gastric wall. Since lymphosarcomas manifest themselves often in the same way as a carcinoma, an exploratory laparotomy and possibly a biopsy at surgery are essential for conclusive diagnosis.

Case History

History

A 70-year-old female was admitted to St. Barnabas Hospital on September 30, 1963, with the diagnosis of carcinoma of the stomach. She had felt well up until about two years before, when she began to have symptoms of epigastric distress. She had lost about 30 pounds during the preceding several years. She weighed 105 pounds and was 5′5″ tall. Her chief complaint was that she had difficulty swallowing solid foods. It is interesting that, while out dining in a group, she had less difficulty swallowing. Soups and other liquids did not give her any trouble. Her appetite was moderate. There was no nausea, vomiting, peptic ulcer complaint, hemoptysis or melena. In 1906 she had had an appendectomy, in 1926 a subtotal hysterectomy (reason unknown), and in 1930 a thyroidectomy (reason unknown). Besides her present gastric complaints she had an indefinite neurological disorder, involving only the lower extremities. She suffered from atrophy and weakness of the legs, walked with a moderately wide base, and had a footdrop.

Laboratory Findings

The patient had been moderately anemic during the preceding years, the anemia appearing to be due to iron deficiency. Her admission hemoglobin was 12.6, erythrocyte sedimentation rate 31 mm./hr., urinalysis essentially negative, and total leukocyte count 7800, with a normal differential.

X-Ray Findings

X-ray studies showed a narrowed antral lumen suggestive of carcinoma of the stomach. Previous X rays taken in July of 1961 had been interpreted as showing no evidence of pathology, although in retrospect an area of narrowing might be made out.

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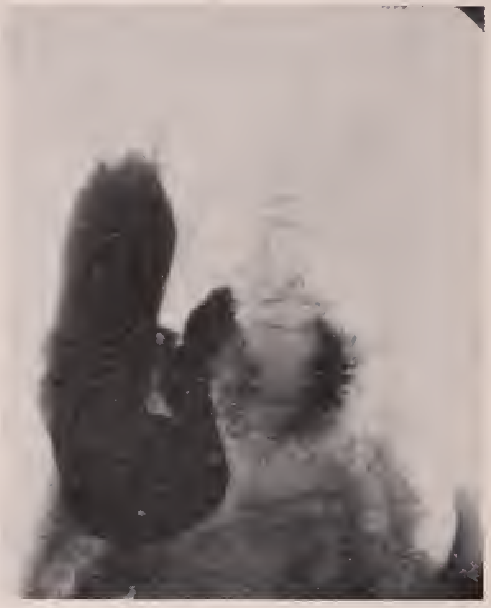

Fig. 1. — 1961, stomach has an unusual fishhook shape.

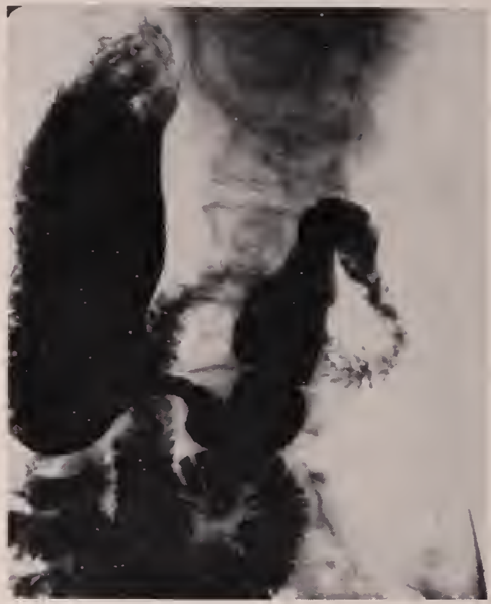

Fig. 2. — 1963, evidence of narrowed lumen.

Physical Findings

On physical examination the patient was asthenic and pale, with a B.P. of 160/90, a pulse of 72/minute, and a temperature of 98.6°F. No visible external abnormalities were found. No lymphadenopathy was found. The abdomen was not distended. There was no tenderness and no masses were palpable. There was no hepato-splenomegaly.

Operative Findings

On October 3, 1963, a laparotomy was performed. A rather large annular tumor was found at the junction of the middle and distal third of the stomach. In addition, the entire stomach seemed to be edematous or involved with tumor. A biopsy of the stomach proximal to the tumor was taken and found to be free of tumor. A subtotal resection of the stomach of the Billroth I type was then performed. Enlarged lymph nodes were found in the region of the head of the pancreas, the left gastric vessels, and the hilus of the spleen, some of which were taken for biopsy and found to be free of tumor.

Pathologic Findings

Pathologic examination of the stomach resulted in a diagnosis of malignant reticuloma with ulceration. An occasional large multinucleated reticulum cell suggestive of a Sternberg-Reed cell was seen. A bone-marrow study eight days postoperatively was free of tumor involvement.

Principles of Diagnosis and Therapy

In review of the literature there is scarcely any disease of the stomach which may not at times mimic the symptoms of early or even late malignant neoplasm. Benign tumors such as leiomyoma, fibroma, etc., often cannot be distinguished clinically from malignant lymphoma and carcinoma, until a histologic study is carried out. Though malignant reticulomas of the stomach may be part of a generalized disease, exploration with resection of the growth is indicated whenever possible in all cases in which the tumor is thought to be primary in the stomach. Resection of the stomach and regional lymph nodes and gastroduodenal anastomosis should be performed. A careful study of the entire alimentary tract should be made to be reasonably certain that there are no additional malignant lesions, because multicentric tumors are relatively frequent. Even when involved regional lymph nodes, which cannot be resected, are present, long survival periods have been reported. The more favorable prognosis in most sarcomas is a strong argument in favor of exploration for all gastric tumors which do not show evidence of metastasis in the hope that an operable tumor will be found.

Radiation therapy after surgery is recommended even in those cases that prove to be inoperable, because lymphosarcomas are radiosensitive.

Chemotherapy is an integral part of the management of lymphosarcomas, when evidence of more generalized involvement is found.

Prognosis

The over-all prognosis in gastric lymphosarcoma is far better than it is for carcinoma. The reported five-year survival shows a higher percentage than in carcinoma. In 7681 cases of adenocarcinoma of the stomach the five-year survival was 4.4 percent; in 47 cases of lymphoma of the stomach it was 44.6 percent.

D. J. A. van Oppen, M.D.
St. Barnabas Hospital, Minneapolis

References

1. Bockus, Henry L.: Gastroenterology 1963. W. B. Saunders Company 802.
2. James, Arthur C.: Cancer Prognosis Manual. American Cancer Society, Inc. 41.

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—Albert Einstein

But it is pretty to see what money will do.—Samuel Pepys' Diary, March 1667

A man must make his opportunity, as oft as find it.—Francis Bacon

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Every noble work is at first impossible.—Thomas Carlyle

About the only thing that comes to him who waits is whiskers.
—Jacob Braude's "Speaker's Encyclopedia"

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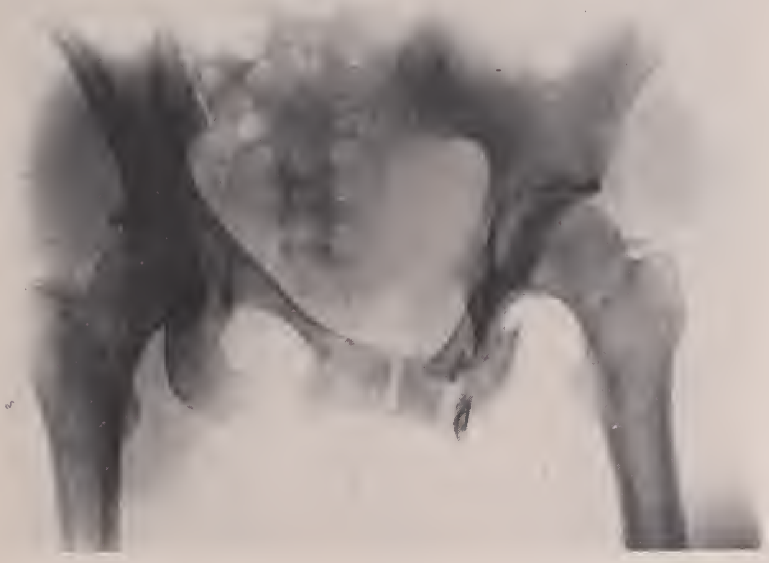

Fig. 1 — Fracture of the pelvis with marked assymetry — Immediately after injury.

The fracture, excluding simple separation of the symphysis pubis, does not lend itself well to manipulative reduction, nor is it frequently necessary; however, it does seem reasonable to attempt correction in the more severe cases so as not to preclude normal obstetrical delivery in women of child-bearing age, and in order to prevent gait impairment. The following case is of interest.

Continued

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A 29-year-old female pedestrian was struck by an automobile on January 16, 1963, and was taken by ambulance to Minneapolis General Hospital. X rays revealed a severe fracture of her pelvis with marked inward displacement of her left pubic rami. Fig. 1. A cystogram revealed no extravasation of contrast media. She was placed supine in bed and with clinical evidence of impending shock a blood transfusion was begun. Over the subsequent eight hours she was given four units of blood. At this time her vital signs stabilized for the first time. However, during the next thirty-six hours three more units of blood were required to maintain her hemoglobin at approximately 12 gm.%. She developed a rather pronounced ileus requiring intravenous feedings and nasogastric suction for the next four days but finally was able to tolerate an oral intake.

Her case was presented to the *Fracture Conference.* It was felt that because the patient was a woman of childbearing age every effort should be made to correct the marked displacement. Recommendation was made for heavy skeletal traction to be applied to each leg and to place the legs in wide abduction. Twenty pounds of weight was applied to each leg through traction on the tibial tubercle. X rays taken the following day revealed significant improvement, but to further correct the medial displacement nine pounds of lateral traction was applied via a towel sling to the right thigh with a pleasing result. Traction was maintained in this fashion for ten weeks, although gradually diminishing the weight to eight pounds per leg. Ambulation was gradually begun at that time with crutches, but soon she was walking without support. On follow-up visit to the Fracture Clinic on June 28, 1963, she was walking normally without pain and her X ray demonstrated satisfactory healing of the fracture fragments in good position. Fig. 2.

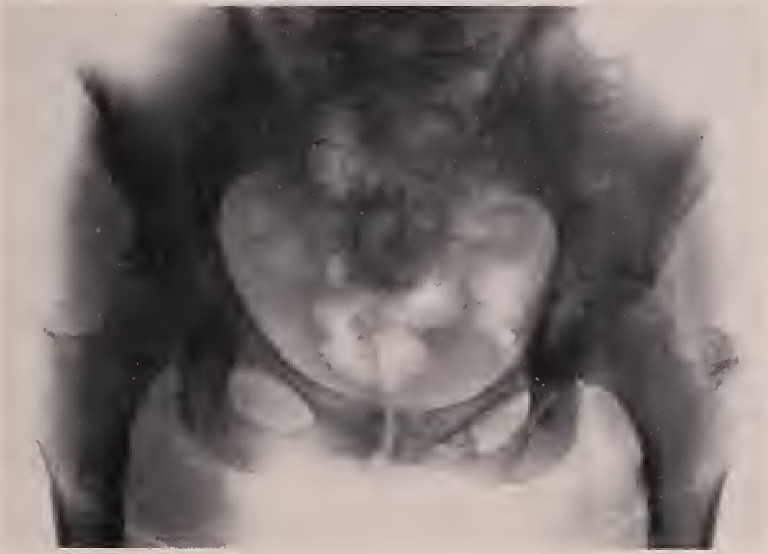

Fig. 2 — Fracture 6 months later.

Experience has shown that lateral crushing fractures causing distortion of the pelvic inlet are most important from an obstetrical standpoint.[1] The case presented demonstrates such a fracture. Perfect alignment of the pelvic girdle following fractures of this magnitude is not commonly achieved, nor is it necessary for normal activity. It would appear that in this instance the fracture has been reduced and has healed satisfactorily, both from an obstetrical and an orthopedic point of view.

Harrison H. Farley, M.D.
Minneapolis, Minnesota

Reference

1. Voegelin, A. W., and McCall, M. L.: Some Acquired Bony Abnormalities Influencing the Conduct of Labor. Amer J Obstet Gynec 48:361, 1944.

One way to reduce motor accidents is to build cars so they can't go any faster than the average person thinks.—American Observer

How Lucas Ray built himself a lake with U.S. Savings Bonds

Like umpteen million other Americans, Mr. Ray loves to fish. Unfortunately, in his part of South Carolina, public lakes are scarce.

Not one to be discouraged, he cashed in a few thousand dollars' worth of Savings Bonds and built his own. He has it well-stocked with crappies, catfish, bass and other fish. And an attractive 4-room cottage sitting beside it (also built by Mr. Ray with money he saved in Bonds).

In case you're wondering, Mr. Ray possesses neither great wealth nor superhuman powers as a saver. He accumulated the money for the lake, fish and cottage by joining the Payroll Savings Plan.

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Grand Rounds

Hereditary Spherocytosis*

A concise definition of hereditary spherocytosis has been given by Kozak,[1] who states, "This is an experiment in nature which has presented hematologists with an unusual opportunity to study the pathophysiology of the spleen. It is a hereditary disease transmitted as a Mendelian dominant trait and characterized by anemia, bilirubinemia, a negative Coomb's test, spherocytosis, increased osmotic fragility, and a positive autohemolysis test." While this is a brief but fairly complete description of the disease, it leaves two erroneous impressions. One is that the spleen is the site of primary pathology, and secondly, that the pathology, symptomatology and physiology of the disease are simple and straight forward. A review of the literature will soon reveal that this is not so, and that the exact role of the spleen, the pathophysiology of the red cell, and the changes in cell fragility after splenectomy as well as the transmission of the disease are not fully explained at the present time.

History

Vanlair and Masius first described spherocytes in 1871 under the title of "la microcythémie," suggesting that the small dark staining cells were corpuscles that were being destroyed. No more note of this was made until 1890 when Wilson described six members of a London family in whom splenomegaly and sallowness or mild icterus appeared as a hereditary condition. In 1893 he included anemia as a feature, but considered the disease to be primarily of splenic origin. In 1910 Minkowski gave a more thorough description of the disease which was followed by Chauffard's report of increased erythrocyte fragility. These two later papers probably contributed to the infrequently used eponym of Minkowski-Chauffard's disease.[8] Following these reports almost all parts of the world have produced literature on the subject.

Etiology

Hereditary spherocytosis is inherited as a Mendelian dominant trait. This was first suggested by Plate in 1913 and Meulengratht in 1921 who investigated seven families. He found that although healthy members of

Continued

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*Presented as a Medical Grand Rounds at Mt. Sinai Hospital, Minneapolis, September 10, 1963.

the family did not appear to transmit the disease, in some cases it apparently developed spontaneously. He and others have attributed this to mutation. This, coupled with the fact that only 24 percent of the offspring of heterozygous marriages developed the disease, suggests that incomplete penetrance occurs with asymptomatic carriers and possibly no abnormal hematological findings. There apparently has been no opportunity to study the disease in the homozygous state, but at least one situation exists where two first cousins, probably heterozygotes, married and produced two miscarriages which may have been the results of lethal homozygosity. Bernard described a family in which there were 13 children, all of whom suffered from hereditary spherocytosis as well as the father. The mother was apparently normal and no history of this disease could be found in her progenitors. He feels that this may have been a homozygous form of hereditary spherocytosis in the father, although no satisfactory family history could be elicited.

The incidence in the general population is thought to be approximately one in 3000,[9] occurring most frequently in Nordic persons but present in all ethnic groups, although quite rare in Negroes. The sexes appear to be equally affected with no tendency toward sex linkage of the trait. Since the disease is congenital, it follows that it is most frequently found in younger individuals. It is rarely seen before the age of four years, although it has been known to occur in newborn infants, causing some difficulty in differentiation from Rh disease or other hemolytic diseases of the newborn. In the other extreme there is a report of a 77-year-old man who was discovered to have the disease when mild anemia and a palpable spleen were found while he was hospitalized for bronchitis.

Symptomatology and Physical Signs

The patient usually presents with the triad of jaundice, splenomegaly and anemia, although any one of these may be the only finding initially. The well known association of gall stones may result in jaundice with an attack of acute cholecystitis and misdirect the physician from the primary disease. Jaundice is usually mild. from 1 to 4 mg. with elevation of the indirect Vandenberg reaction, and is usually not present in infants. It is thought that the elevated bilirubin is generally not due to an excessively high rate of hemolysis but rather to the relative inefficiency of the liver in handling bilirubin. Uncommonly bilirubinuria is present and is usually associated with cholelithiasis.

Anemia

The anemia can be either chronic or acute and is more commonly absent than severe. Usually the hemoglobin is between 7.5 and 14.0 gm.%. The increased erythropoesis generally compensates for the increased hemolysis.

Splenomegaly

The spleen is almost always enlarged and occasionally is the only sign of the disease. Young, Izzo and Platzer describe six out of 29 patients without a palpable spleen. Most investigators agree, however, that even when the spleen is not palpable, it is enlarged to at least a moderate degree. In children splenomegaly is much more common and is considered an almost constant finding.

Gall Stones

Two other findings are leg ulcers and gall stones, the former of which is considered to be uncommon and not diagnostic of the disease. Gall stones have been shown to be present in five percent of children under ten years of age and approximately 50 percent of older individuals with the disease. The cause is thought to be increased concentration of bile pigments with the formation of pure pigment stones.

Hematology

Hyperchromic Anemia

The usual picture is a microcytic hyperchromic anemia with spheroidal cells on peripheral smears, or better seen in a thin saline suspension.[3] The red blood cell population is frequently described as double, with varying quantities of normal and abnormal cells present.

Spherocytes

The greatest number of red cells with a spherocytic configuration are seen in blood from the splenic vein. The severity of the disease seems to be directly proportional to the number of spherocytes present. Reticulocytes are also frequently present in large numbers with a direct relation to the anemia and rate of hemolysis. They may be infrequent or absent during crises. The spherocyte is typically a small dark staining cell.

Increased Osmotic Fragility

More helpful than the morphology of the cells, however, is the change in hemolysis of incubated cells and in those cells placed in saline suspensions of varying tonicity. First described in 1907 by Chauffard was the phenomenon of increased osmotic fragility of the patient's cells. Hemolysis of previously incubated cells (37° for 24 hours) in hypotonic solutions of varying strength, and autohemolysis of cells after 48 hours of incubation with and without glucose, have added to the diagnostic values of the older test. The cells characteristically hemolyze in a solution of reduced tonicity, giving a typical curve when plotted as the percentage of hemolysis occurring at different concentrations of saline with a controlled time exposure. This is the so-called "tailed normal hemolysis curve" with the peak shifted to the left (on a scale in which tonicity of the fluid rises from 0 to 0.9%) (Fig. 1). The same curve with incubation is further shifted to the left with a greater tailing. Incubation of the cells in isotonic saline or serum results in increased autohemolysis after 48 hours, but the addition of glucose inhibits this effect and further distinguishes hereditary spherocytosis from other hemolytic diseases with autohemolysis. Other findings are increased mechanical fragility, a short red blood cell survival time with tagged cells using chromium 51 and rarely serologic changes suggesting some type of autohemolysis, or isoagglutination.

Urobilinogen

The fecal urobilinogen is characteristically elevated but may vary, frequently dropping to or below normal levels during a crisis. Watson states that the average daily excretion is between 136 and 2,475 mg. per day. Urine urobilinogen is usually normal or only slightly increased unless complicating factors such as liver damage are present. If the cells of a

Continued

patient with spherocytosis are transfused to a normal individual with a normal spleen the curve is much the same as that seen in patients with the disease. However, if the individual to whom they are transferred has had a splenectomy, the cell survival time approaches that of normal cells.

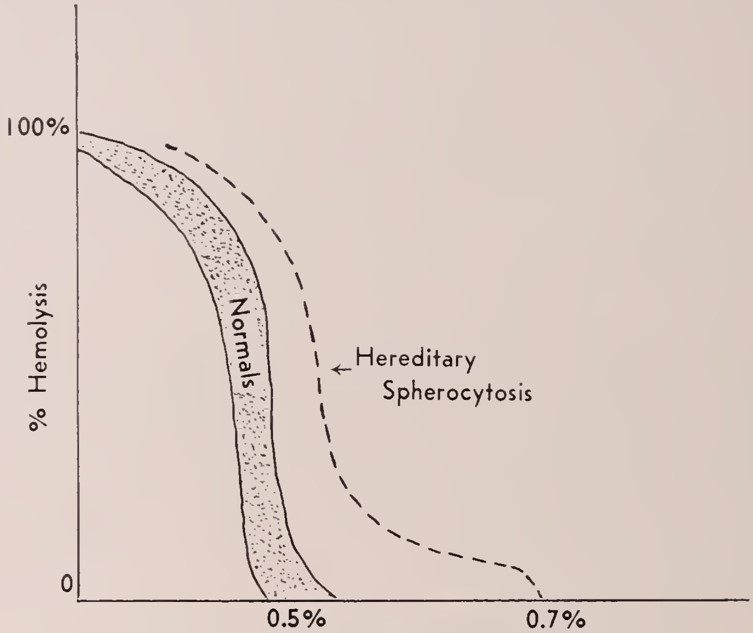

Fig. 1 — Osmotic fragility — Dacie[2]

Types of Disease

Mild forms of the disease have been reported in which no anemia is present and polycythemia occasionally occurs in some cases. Some divide the disease into three groups: (1) so-called complete or typical forms, (2) the compensated form in which 35 percent have no anemia, 40 percent are without jaundice, 30 percent without splenomegaly and ten percent without increased fragility, and finally (3) a mild form, called "leichte heamoalytische Konstitution."

The Mild Form

This latter group includes those with minor hemolytic tendencies, minor variations in the blood picture, minor increases in fragility and slight or occasional chemical jaundice with or without splenomegaly. Dacie feels that considerable care must be taken in diagnosing the milder forms of this disease, and if no evidence of increased fragility can be elicited other diagnoses should be considered. It is in this group that autohemolysis studies and incubation cell fragilities are extremely helpful.[10] Atypical forms are found as well as mild forms which may either have unusual blood findings or react abnormally to splenectomy. Other atypical cases may be produced by combinations of hemolytic diseases and anemias, such as sickle cell disease, thalassemia, pernicious anemia and acquired hemolytic anemia, all of which have been reported but not conclusively proven.

The Crisis

A characteristic of the disease is the crisis, which consists of increased anemia with associated fever and abdominal pain. Minor crises frequently follow low-grade infections and seem to be due to increased hemolysis with a mild marrow hypoplastic component. The major crises seem to be almost always due to a marrow aplastic crisis and frequently are not associated with jaundice.

It is known that many members of a family may be affected at one time or more commonly in succession, suggesting an infectious process. One family of five children has been reported with eight or more days between the onset of the crisis and all of whom began with an apparent upper respiratory infection.[1,6] It has also become evident that increased hemolysis with jaundice is not the cause of the crisis. Many if not all patients have been found to have lower reticulocyte counts during the early phases of the crisis and some have been found to have aplastic or at least depressed bone marrow. The most complete paper on this subject was by P. A. Owren, who considered the crisis to be caused by aplasia of the bone marrow.[6] His group had one case in which there was an opportunity to observe the development of the bone-marrow changes, which he describes as primarily erythropoetic aplasia, although peripheral blood pictures reveal depression of all elements during the crisis. All cases appeared to follow a similar pattern (Fig. 2) in which the hemoglobin and red blood count remained low or actually dropped until after the white count was returning to normal or became elevated. It should be noted that the white count varied between 4,000 and 40,000, which he related to either the aplastic phase of the disease or to the early recovery in which the leukocyte production recovered prior to the return of red cell production.

Elevated Serum Iron

Serum iron was uniformly elevated during the crisis, with a rapid drop after the onset of recovery, indicating lack of utilization of the iron and

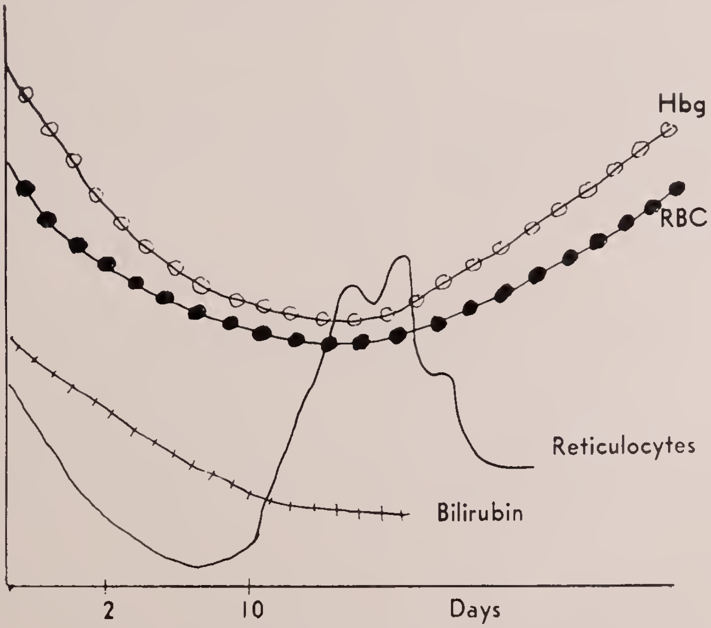

Fig. 2 — During the Crisis — from Owren[6]

suggesting decreased hemoglobin incorporation during the crisis. Owren gives no reason for the onset of the crises other than that they might be, as previously stated, of infectious origin.

Dameshek agrees that the crises are a result of decreased production or release of red blood cells, but due to arrest rather than aplasia of the bone marrow. He suggests the possibility that immune mechanisms are involved and that the primary cause may be hypersplenism with depression of the marrow similar to that seen in cirrhosis of the liver.[5] Battle, on the other hand, supports Owren and cites two cases of marrow hypocellularity with proerythroblastic arrest.[4] He also feels that the lack of jaundice in acute crises supports Owren's theory. The difficulty in coming to a definite conclusion as to the exact mechanism is related to the transitory changes in the marrow and the few opportunities to study the marrow early and repeatedly. It is most likely that the crises are brought about by an upset in the delicate balance between compensatory erythropoesis, hemolysis, and temporary arrest or depression of the marrow elements.

Bone-Marrow Hyperplastic

The bone marrow is usually found to be hyperplastic with decreased fat and increased marrow volume, if examined during the asymptomatic or static stages of the disease. The hyperplasia contributes to the increased marrow spaces and may result in X-ray changes in the bones. These changes usually are widening of the bones which contain active marrow but are not considered to be pathognomonic of hereditary spherocytosis.[11]

The Spleen

The spleen is enlarged and may weigh as much as 2000 grams. It is smooth, dark red in color and deeply congested. The characteristic changes on microscopy are relative emptiness of the sinuses with congested pulp. There are no infarcts, and hyperplasia of lymphoid tissue is not evident.

Differential Diagnosis

The differential diagnosis includes other hemolytic anemias and hemoglobinurias. A helpful table has been reproduced from Wintrobe's recent edition of *Clinical Hematology* and is included in the appendix.

Treatment

Splenectomy

Once the diagnosis is established, splenectomy is the treatment of choice. Anemia rapidly disappears and many of the hemological findings return to or toward normal after splenectomy. The only contraindications to splenectomy are young age and acuteness of the crisis. Finland believes that after splenectomy, infection is frequent in those children under three years of age and may result in 10-21 percent infections with a 4-8 percent mortality in this group.[9]

Antibiotics

Most authors agree that patients should be treated with antibiotics for at least one year if splenectomy is performed before the age of three, many extending this prophylaxsis up to the age of five. Early splenectomy is indicated if the patient is a good surgical risk, to prevent the later complications of cholelithiasis and the danger of a severe anemia, which may be complicated by serious infections or may in itself be fatal. Rare instances of relapse after splenectomy have been reported but most of these appear to have been misdiagnosed cases of other hemolytic diseases. There are, however, occasional cases of proven disease where, either as a result of congenital arrests or splenic seeding at the time of surgery, accessory spleens have been found to be the cause of relapse. It is the consensus of opinion that splenectomy should be carried out as soon as the patient can tolerate the procedure and is more than three years old.

Blood Transfusions

Blood transfusions are indicated if the anemia is severe, and a short delay before surgery is acceptable to allow the patient to recover from a severe marrow aplastic phase. Cell survival times return toward normal after splenectomy, although spherocytosis persists and may increase or decrease. The osmotic fragility test usually is improved, and the tail of the curve thought to be due to the splenic incubated cells disappears. The 24-hour fragility is increased, however, because of the population of abnormal cells which formerly had been destroyed by the spleen.

Pathophysiology

The primary defect in hereditary spherocytosis appears to be in the red cell.

Enzymatic Deficiency

The exact nature of this difficulty is unknown, although evidence points toward enzymatic deficiency in the regulation of glucose metabolism. It is known that the red cells are abnormally sensitive to glucose deprivation. Other investigators have shown that adenosine, quanosine, and inosine all reduced hemolysis similar to glucose, presumably because of their properties of furnishing adequate high energy phosphates. This supports the theory that deficient phosphate metabolism interfering with energy bonding and glucose metabolism is a primary defect. Other studies[7,16] have been done on cell membranes and suggest abnormal phospholipid metabolism with increased concentrations of lysophosphatidyl ethanolamine and lysolecithins which have been shown to cause sphering of cells in normal patients.

The Spleen

The role of the spleen appears to be primarily that of a filter and site of incubation of the abnormal cells.[3] The action of splenic incubation is thought to be similar to the 48-hour hemolysis test, since abnormal cells seem to be held in the spleen longer than normal cells.[1] This is supported by the finding of an increased percentage of abnormal cells in splenic blood of spherocytic patients (in some up to 30 percent) as well as studies of the movement of tagged cells through the splenic circulation. It is thought that phosphate esters become depleted during splenic incubation and the brief period of recirculation is not enough for recovery of these abnormal cells.[17]

Continued

TABLE 1
Comparison of Findings in Five Types of Hemolytic Disease

	Hereditary Spherocytosis	Hemolytic Disease		Paroxysmal Hemoglobinuria	
		Auto-immune	Iso-immune	Cold*	Nocturnal
Inheritance	Mendelian dominant	—	—	—	—
Thrombophlebitis	Uncommon	Occurs	None	None	Common
Vasomotor disturbances	None	In cold type	Shock	Common	None
Response to:					
Splenectomy	Excellent	Irregular	None	None	None
Adrenocorticosteroids	None	Good	?	?	Contraindicated
Spherocytosis	Characteristic	During crisis chiefly	In anti-A and B; not in anti-Rh	Unusual	None
Fragility:					
Osmotic	Inc., esp. after incubation	Normal or inc. (in active phase)	Normal in anti-Rh Inc. in anti-A and B	Normal	Normal
Mechanical	Increased	Inc. in crises	Normal	Normal	Normal
RBC survival					
Normal cells in pt.	Normal	Decreased (curve exponential)	Normal	Same as pts.' cells	Normal
Pt. cells in normal	Depressed	Normal or sl. dec.	Normal	Normal	Decreased
Hemoglobinemia	None	May occur	May occur	In attacks	In active phase
Methemoglobinemia	None	May occur	None	In attacks	In active phase
Coombs': Direct	Usually negative	Positive	Positive (neg. in ABO)	Positive (after sensitization in the cold)	Negative
Indirect	Negative	Positive	Positive		Negative
Auto-agglutinins:					
Warm Complete	None	Rare	None	None	None
Incomplete	None	Frequently present	Present (in anti-Rh)	None	None
Cold	None	May be present	None	Minimal or none	None
Auto-hemolysins	None	Rare	None	Characteristic	None
Acid hemolysis	None	Sometimes	None	None	Characteristic
Hemosiderinuria	None	Moderate	May occur	Following attacks	Characteristic

*Type associated with syphilis

from Wintrobe, M. M.: **Clinical Hematology** (Lea & Febiger) 1961, 5th ed., p. 621

Case Report

The patient is a 23-year-old woman who was admitted to the Mt. Sinai Hospital on 7-14-63. She was found to have anemia following the discovery of an anemia in her daughter. On further study both the mother and daughter were found to have hereditary spherocytosis and family history revealed similar difficulties in the patient's father, a brother and a niece. The patient had no overt manifestations of the disorder and had had no episodes of severe anemia or jaundice. She did feel tired on waking in the morning and tired easily with exertion. The present admission was for further laboratory investigation and consideration for splenectomy.

Past medical history was essentially negative. She had had whooping cough as a child. Operations included tonsillectomy, appendectomy and two Caesarean sections. There was no history of blood transfusions or allergies. System review was negative. The patient had had easy bruisability but no bleeding tendencies.

On admission the patient appeared to be in good health, with no evidence of jaundice or pallor. Blood pressure was 138 88. The skin was clear except for white striae on the upper legs and abdomen. Eyes, ears, nose, and throat were negative. The cardiorespiratory system was negative. The spleen was not definitely felt to be palpable by any of the examiners prior to surgery. Back and extremities were normal. There was a midline abdominal scar. Pelvic organs were within normal limits. Neurological examination was negative.

Laboratory examinations revealed the following: Hemoglobin 12.0 gm.%, erythrocytes 3,760,000, leukocytes 6,800 with 61% neutrophiles, 30% lymphocytes, 4% monocytes, 5% eosinophiles. Sedimentation rate 15 mm./hr., hematocrit 35, reticulocyte count 2%, bleeding time one minute, capillary clotting time 3 min., prothrombin time 13.3 sec. control, 16.2 sec. patient. Red cell morphology revealed slight anisocytosis, slight polychromasia, basophilic stippling, and spherocytes were present. Red cell indices: MCH 32, MCV 96, MCHC 33, VI 1.11, CI 1.08, SI 1.00. The osmotic fragility test was positive. The serum bilirubin was total 1.1 mg.% and one min. 0.3 mg.% Urinalysis was negative. VDRL routine negative on admission. Fasting blood glucose was 92 mg.% urea nitrogen 11 mg.%, and cholesterol 163 mg.%. Coomb's tests were negative both direct and indirect. Urine urobilinogen was 1.9 mg. in a two-hour specimen collection. A platelet count was reported as 223,000 on the morning prior to surgery. The platelet count rose to a high of 550,000 four days after splenectomy. X rays revealed a normal abdominal scout film, normal chest X ray and a normally functioning gall bladder without stones.

On 7-17-63 a splenectomy was performed under general anesthesia. The spleen was judged to be 2 times normal size and no accessory spleens were found. One unit of blood was administered during the surgery. The postoperative course was uneventful until the ninth day when the patient developed right calf pain and a diagnosis of thrombophlebitis was made. Anticoagulants were started with a satisfactory recovery over a 10-day period.

The pathologist reported the spleen to weigh 232 grams with grossly normal appearance. The cut surface was dark red and trabeculae and corpuscles were only faintly visible. Microscopic examination revealed the Billroth cords to be filled with packed erythrocytes in contrast to the empty sinuses lined by prominent littoral cells.

Summary

In summary we must conclude that this is a hereditary disease transmitted by a modified Mendelian dominant mechanism. The primary difficulty is a poorly understood defect in the metabolism of red blood cells, probably as a result of inadequate phosphorolysation by glycolytic enzymes. The symptoms all relate to acute and chronic hemolysis as well as aplasia and/or depression of the bone marrow with resultant severe anemia. The treatment is splenectomy which usually allows the patient to have a normal life and stops the symptomatic phase of the disease, although the red cell defect persists.

D. A. Bergeron, M.D.
Mt. Sinai Hospital

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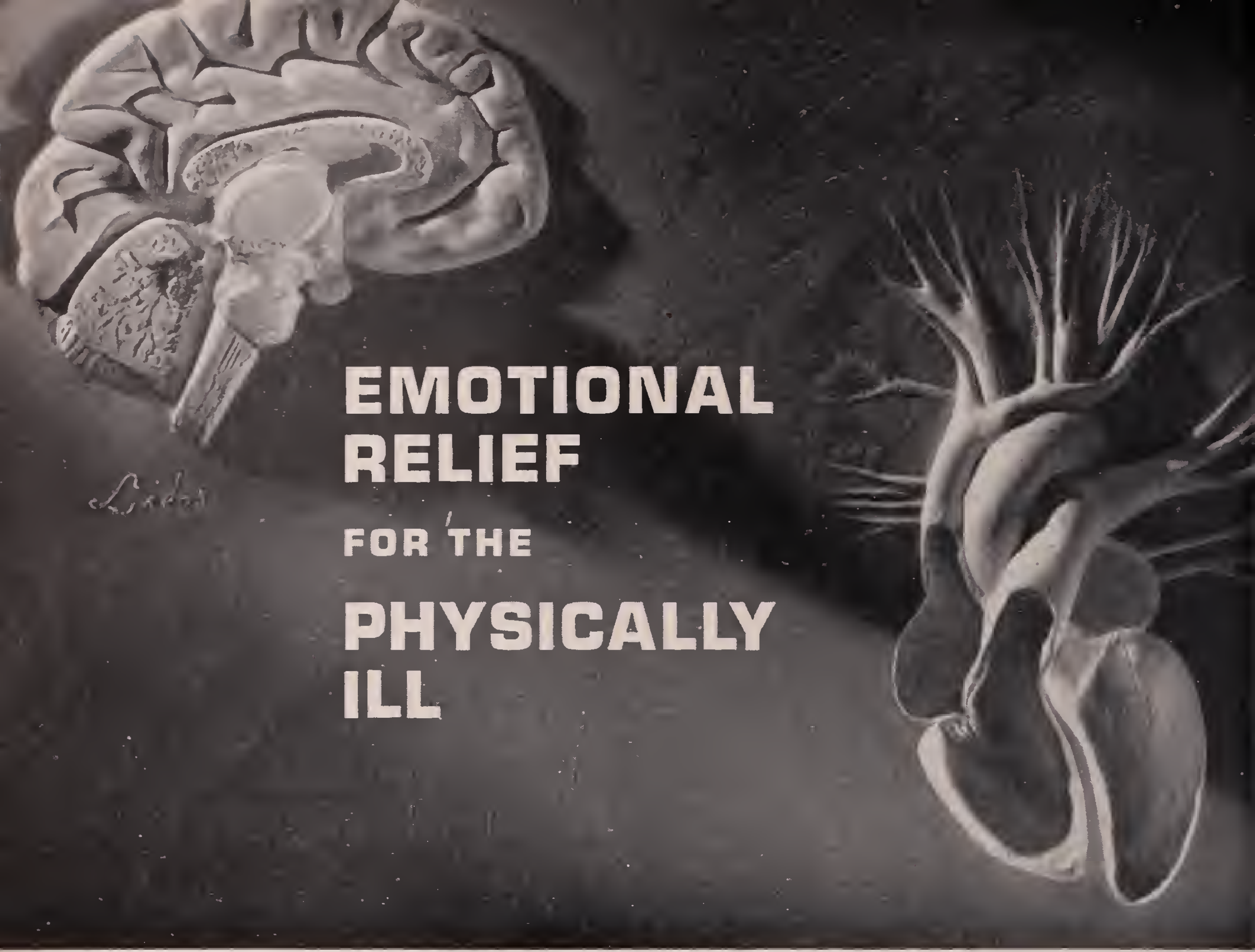
13-17 Can be obtained from Grand Rounds Editor at Mt. Sinai Hospital.

Economize

He who will not economize will have to agonize.—Confucius



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Abstracts, Briefs and Commentaries

STAPHLOCOCCAL ENTEROCOLITIS

The authors have made a study or analysis of 155 patients with staphylococcal enterocolitis following antibiotic therapy on the surgical service. They have evaluated such conditions, as pre-existing diseases, bacterial etiology and treatment. There were 48 deaths 20 of which were due to sepsis. Eight cases constituted hepatic failure after the enterocolitis had subsided. Four were due to cardiac failure, others to pulmonary emboli, uremia, and miscellaneous problems. Seven of the deaths seemed directly attributable to the enterocolitis.

The most prominent symptoms were diarrhea, bloody stools, shock, abdominal pain, and occasional vomiting. The largest group of patients in the study had pre-existing disease of the GI tract requiring operations, but one third had no operations.

The majority of the patients had received penicillin in combination with some broad spectrum antibiotic, usually Achromycin, prior to the development of the staphylococcal enterocolitis. However, 44 patients developed the problem after treatment with neomycin. Of these thirty-two were treated with neomycin in preparation for operation. The staphyloccus aureus isolated from the stools of these patients was commonly most sensitive to novobiocin and bacitracin. Less than half of the organisms were sensitive to erythromycin.

In the discussion, the mechanical cleansing of the bowel as a fundamental step prior to surgery is favored by some over any antibiotic preparation.

This article serves as a review of the causes and symptoms in the management of an extremely serious complication of our modern therapy.

J. H. Strickler, M.D.
Minneapolis, Minn.

William A. Altemeier, M.D., Robert P. Hummel, M.D., Edward O. Hill, Ph.D. Ann Surg Vol 157:847 June 1963

PULMONARY ARTERY BANDING

Pulmonary banding is a temporizing procedure for reducing the diameter of the pulmonary artery and the flow of blood into the lungs in congenital heart lesions. By reducing the left to right shunt, "banding" reduces the work of the left ventricle and also the injury to the pulmonary arterioles. The procedure

Continued

is used routinely in infants with congenital heart lesions and heart failure as part of the two stage approach to corrective surgery.

The authors describe their method. They monitor pressure as a guide to the degree of banding, i.e. one half of the right ventricular pressure.

Two types of patients were submitted to operation:

(A) Group I — 18 patients with ventricular septal defect. The indication was intractable heart failure. Severe pulmonary hypertension was present in eight. One patient died. The others were improved.

(B) Group II — 20 patients with complicated heart defects. The indications for operation were intractable heart failure, multiple episodes of pneumonia, and general growth failure. Seven patients survived. Four are doing well.

"Banding" should not be done if the pulmonary hypertension and arteriolar resistance causes reversal of the shunt.

The authors conclude that pulmonary artery banding is a worthwhile temporizing procedure in patients in intractable heart failure with isolated ventricular septal defect or single ventricle. The procedure has proven disappointing in complicated congenital heart defects.

The benefit of this procedure is directly correlated with the type of congenital heart lesion. Accurate clinical diagnosis, even if cardiac catheterization and angiography is needed, is, therefore, of utmost importance in all infants suffering from cardiac decompensation.

Jerome T. Grismer, M.D.
Minneapolis, Minn.

Craig, T. V. and Sirak, H. D.: Pulmonary Artery Banding. An Analysis of 38 Cases. J Thorac Surg: 45:599, 1963

EMBRYONAL CARCINOMA OF TESTIS

Trophocarcinoma (embryonal carcinoma) is the most highly malignant germ-cell tumor of the testis; three-fourths of the deaths occur within the first year. There is little relation between histological type and prognosis except for chorioepithelioma, which was fatal to all patients in this series. A direct relation was found between stage and prognosis. Only patients with no clinical or radiographic evidence of metastasis are potentially curable. Approximately 10% of trophocarcinomas are so small as to be difficult to detect. Cures of this variety are rare, as the diagnosis is usually based on widespread metastasis at the time of first examination. In patients without clinically detectable metastasis, surgical exploration disclosed metastatic trophocarcinoma in 62% of the cases. This is contrasted with approximately 12% for seminoma. The optimum tumor lethal dose for most trophocarcinomas ranges from 3,500 rads in 10 days to 4,500 rads in 40 days. These doses result in mild to moderate radiation injury to the gastrointestinal tract in 25% of the cases when cross-fire techniques are used. Supervoltage rotation irradiation has eliminated these injuries. Current treatment entails a preliminary test dose of 1,000 rads to the testis, orchiectomy, retroperitoneal node dissection, and postoperative irradiation. There is growing evidence, however, that omission of the node dissection might increase survivals. Eight of nine patients so treated have survived more than five years. In 83 consecutive, unselected, pure trophocarcinomas, the absolute five-year survival rate was 30%. Removing the chorioepitheliomas would increase this rate to 35%. Among 48 patients without clinically demonstrable metastasis, the five-year survival rate was 51%; excluding deaths from radiation injury, the survival rate would be 62%.

Courtesy of References and Reviews
Journal of the American Medical Association

Friedman, M., and Di Rienzo, A.: Radiology 80:550 April 1963

CLOSURE OF ATRIAL SEPTAL DEFECTS

The authors describe the interesting problem of congenital atrial septal defects of long duration with secondary pulmonary hypertension and the shunting of blood from right-to-left as well as left-to-right. As they indicate the mortality in the surgical repair of this lesion has been very high. Utilizing laboratory work which indicated that atrial septal defects in dogs were closed spontaneously, the authors performed surgical repair with perforated prostheses in four patients.

They presented the preoperative and postoperative studies which indicated that the perforated prostheses acted as a decompression for the right ventricular hypertension during the time of stress. All of the patients survived. In two, there was complete closure of the defect in a period of three weeks. The patients continued to do well even though the pulmonary artery pressure remained high. Clinically, there was improvement in exercise tolerance in all four patients. The pulmonary artery pressure tended to fall although it was still elevated.

The use of this technique is reserved for those individuals who have pulmonary hypertension, right-to-left shunt, but still evidence of a left-to-right shunt of some degree.

This same technique might be applied to other congenital defects in which the function of the right ventricle is grossly impaired as in Ebstein's anomaly or hyperplasia of the right heart. This also might be true for gradual closure of ventricular septal defects in which there was right-to-left as well as left-to-right shunting.

Jerome T. Grismer, M.D.
Minneapolis, Minn.

Braunwald, N. S., and Morrow, A. G.: "The Delayed Closure of Atrial Septal Defects with Perforated Prostheses." SG&O 116:579, May 1963

SEMINOMA

An analytic review is presented of 56 cases of seminoma of the testis, with particular reference to the areas of tumor extension and the reasons for failure to cure. The following conclusions are drawn: (1) Seminoma is a consistently radio-sensitive tumor. Local control of the disease may be anticipated by doses in the range of 2,000 to 3,000 rads delivered via standard orthovoltage techniques over treatment periods of four to six weeks. (2) Failure to cure seminoma by irradiation can be explained in almost every instance by inadequate coverage of areas demonstrably or potentially involved by tumor. (3) When seminoma is shown in any region, irradiation in effective dosage should be delivered to both that region and to the next successive area of lymph node drainage. (4) Neither volume nor extent of tumor involvement is a contraindication to intelligent aggressive radiation therapy, which will be rewarded by an unbelievably high cure rate. Seminoma is radiocurable in every case if areas of tumor involvement are accessible to effective doses of irradiation. This condition is met in nearly every instance.

Courtesy of References and Reviews
Journal of the American Medical Association

Johnson, G.: Radiology 80:539 April 1963

Continued

SALICYLATES AND BLEEDING

The topical irritant action of salicylates on the mucous membranes of the mouth was observed in 26 human subjects. The buccal mucosa appeared white and opaque, and it sloughed off in the area where all forms of acetylsalicylic acid tested had been in contact for one-half hour or longer. There were no gross detectable mucosal changes when 4'-hydroxyacetanilide (4HA) was placed between the lip and the gum of 21 human subjects. Localized mucosal damage was produced in 38 of 45 anesthetized cats in which direct mucosal contact with acetylsalicylic acid and its compounds was permitted for two to three hours, by placing the tablet of medication in the stomach through a gastrotomy. Multiple foci of acute mucosal necrosis were the most striking findings. No gross or microscopic changes were noted in the gastric mucosa in the 27 cats in whom 4HA was used. Focal necrosis may contribute to occult bleeding, and, if repeated frequently enough over a long period of time, a so-called refractory anemia may ensue. If the focal necrosis occurs in a susceptible individual, a massive hemorrhage may follow the ingestion of salicylates. Patients who appear to be susceptible (peptic ulcer diathesis, hypertrophic gastritis, esophagitis, diverticula of upper gastrointestinal tract) to the topical irritant or hemorrhagic effects of acetylsalicylic acid should be warned of these hazards and cautioned not to use salicylates in any form.

Courtesy of References and Reviews
Journal of the American Medical Association

Roth J., Valdes-Dapena, A., Pieses, P., and Buchman, E.: Gastroenterology 44:146 Feb 1963

THORACOTOMY IN PATIENTS OVER THE AGE OF SEVENTY

Eighty-nine operative records of patients over seventy years of age who underwent a thoracotomy (excluding limited or closed thoractotmies) were reviewed. Sixty-four patients were 70-74 years old (twelve died); twenty were 75-79 years old (seven died) and five were over 80 years of age (three died). Sixty-five patients had neoplasms of the lung or esophagus. Of these, nine were females. The remaining twenty-four patients had non-neoplastic lesions of the lung, diaphragmatic hiatal hernia, aortic aneurysm, esophageal strictures, or Stokes-Adams syndrome.

Most of the patients had stigmata of hypertensive or arteriosclerotic heart disease and an increased chest diameter suggestive of emphysema. Of eighty-eight preoperative electrocardiograms, fifty-four were abnormal. The mortality in this group was 29.6% as compared to 11.4% in those patients with normal electrocardiograms. No specific objective pulmonary function was routinely done.

Postoperatively, cardiac arrhythmia and cardiac failure, and retained bronchial secretions were the most important contributing causes of morbidity and death. Other causes included anastomotic intestinal leaks and bronchopneumonia. There was one cardiac arrest in the operating room.

Preoperative prophylactic digitalization seemed beneficial in preventing cardiac arrhythmia and subsequent decompensation.

Over all hospital mortality in the eight-nine patients was 25%.

The operative and hospital mortality is not appreciably higher in this group of patients than in younger patients undergoing similar surgical procedures. Age alone therefore is no contraindication to operation on the thorax.

J. T. Grismer, M.D.
Minneapolis, Minn.

Heilbrunn, A., Hardin, C. A.: J Thor Cardiov Surg 46:13 July 1963

ATHETOTIC CEREBRAL PALSY

The authors state that "prevailing opinion still holds that athetotic cerebral palsy has multiple causes in common with other types of cerebral palsy." They note that this opinion has been changed at least in part by Gerard's recognition of a frequent history of neonatal jaundice in patients with athetotic cerebral palsy. The present report is based on a study of 27 cases of athetotic cerebral palsy for which adequate hospital records were available for review. Athetosis was defined as "writhing, rotary movements of the extremities and trunk which could not be controlled by the subject, interfering with his motor functions." Cases of athetotic cerebral palsy were found to fall into two types. All seven patients of one type, which was characterized by deafness and impairment of upward gaze, had a history of neonatal jaundice. The 17 patients with the other type, associated with hypertonicity and Babinski signs and without deafness and upward gaze paralysis, all had a history of asphyxia neonatorum. Two cases were found to have mixed clinical types; both cases had a history of asphyxia neonatorum and one had been jaundiced.

Peter J. Dyck, M.D.
Rochester, Minn.

Churchill, John A., and Colfelt, Robert H.: Etiologic Factors in Athetotic Cerebral Palsy. Arch Neurol 9:400 October 1963

ANEMIA OF MALIGNANCY

In malignant disease often none of the usual causes of anemia including blood loss, increased blood destruction, myelophthisis, or hematotoxic effects of drugs can be demonstrated. The anemia is usually mild to moderate, is frequently normochromic and normocytic, and erythrokinetic studies have not clarified the mechanism. Serum iron and iron-binding capacity are usually low and iron administration generally fails to correct the anemia in the absence of blood loss. In an attempt to better explain the mechanism of the anemia, the author has investigated the reutilization of iron released from normal processes of red cell destruction in vivo. High-count iron tagged hemoglobin was injected intravenously into a series of patients with a variety of malignancies and into normal controls; and studying "maximum reutilization of iron" the values for reutilization in the patients with malignancy were all lower than those for the normal control. This is of significance, since the reutilization of iron provides a greater supply of iron to the bone marrow per unit of time than does iron absorbed from the gastrointestinal tract. The authors do not know the mechanism responsible for this defective reutilization. It is similar to the defect observed in the anemia of infection, rheumatoid arthritis and some other inflammatory states.

This is an interesting set of observations but the authors have not been able to unravel the basic mechanism responsible for them in their attempt to gain further understanding of the anemia of malignancy.

Robert A. Green, M.D.
St. Louis Park Medical Center

Haurani, F. I., Young, K., Tocantins, L. M.: Re-utilization of Iron in Anemia-Complicating Neoplasms. Blood 22:73, July 1963

Continued

VITAMIN A INTOXICATION

Skeletal damage consisting of growth retardation and premature closure of the epiphyses was observed in varying degrees in seven children who exhibited signs of severe chronic Vitamin A poisoning. Three of the children suffered alterations of skeletal development which are probably irreversible, resulting in unequal leg lengths; when damage to cartilage cells is permanent, full longitudinal leg length cannot be attained. The author says that of the seven children (six of whom were hospitalized) determinations of Vitamin A blood levels were made in only two; in the others the diagnoses were based entirely on clinical and radiological findings showing typical cortical hyperostosis. In five cases the Vitamin A administration was halted and low Vitamin A diets were instituted. The Vitamin A concentrates had been given at home in doses higher than had been prescribed. The author suggests that Vitamin A metabolism may differ among individuals, and that the notion that 200,000 units of the vitamin can be given safely every day is highly questionable. Considering the possibility that carotenoids in the diet may be converted to Vitamin A, perhaps the supplementary administration of concentrates should be related to dietary intake.

The children, six girls and a boy, ranged in age from thirteen months to seven years. Three of the children had been referred to the orthopaedic service because of a leg-length discrepancy; other symptoms included leg and skeletal pain, unsteadiness of legs or inability to walk; irritability and crying, swelling in the temporal region, loss of appetite, and loss of hair. Where X rays were made of forearms and knees, changes observed included hyperostosis involving the ulna and tibia with long bone epihyseal irregularity and sharpening of metaphyseal margins. Later on there was definite thinning of the epiphyseal plate, especially at the knees because of weight bearing. The distal femoral metaphysis broadened, flaring out, in the words of the author, to a pagoda-like appearance. A mirror-like image occurred in the adjacent tibial metaphysis. There was also thinning of the cortex of the bone around the epiphysis. Further, the author reports, there were instances of broadening of the shafts of the long bones and alteration of tubulation. In the more severe cases, the epiphyseal cartilaginous plates become very narrow, with premature ossification. It is quite likely, the author adds, that epiphyseal plates of the vertebrae areal are also affected in a similar fashion, with interference of normal development of the segments.

Discontinuance of supplementary dosages of Vitamin A resulted in subsidence of symptoms, but, as noted above, skeletal alterations in several cases were considered irreversible. The author discusses orthopaedic management case by case where it was indicated, not reviewed here.

Courtesy of Medical Abstract Service
Berwyn, Illinois

Pease, C.: JAMA 182:980 Dec. 8 1962

Opportunity

The reason so many people never get anywhere in life is because, when opportunity knocks, they are out in the back yard looking for four-leaf clovers.

—Walter P. Chrysler

Indispensable

Make yourself indispensable, and you will move up. Act as though you are indispensable, and you will move out.—Jules Ormont

BOOK REVIEWS

THE THYROID AND ITS DISEASES — Means, James A., M.D., DeGroot, Leslie J., M.D., Stanbury, John B., M.D.; McGraw Hill Book Co., Inc., New York, 3rd Edition, Price $15.95, 618 pages.

This is an extensive monograph on the clinical phases of the thyroid and its diseases.

The book is well bound. The references at the end of each chapter are adequate and inclusive. In twenty chapters it covers a multitude of thyroid diseases.

It represents the tremendous experience of some well qualified men, and though it is a bit difficult to read because of its verbosity and compound sentences it represents an excellent supply of knowledge.

There is a tendency to use alphabetical abbreviations, some of which defy interpretation even in the medical abbreviation dictionary. An example of this is "a large and relatively sequestrated pool of PBI in the thyroid, after the administration of I^{131}, disclosed a quantity of MIT and DIT but only traces of parathormone (PTH)." For the uninitiated a repetition of this could well discourage many reading physicians.

An additional number of illustrations might have relieved the monotony of uninterrupted type.

Carl O. Rice, M.D.
Minneapolis, Minn.

OCCUPATIONAL HEALTH AND MANTALENT DEVELOPMENT — Dr. Robert Collier Page, M.D., Physicians Record Company, Berwyn, Illinois, 1963. 680 pages. $18.50

This book, a major contribution to its field, discusses numerous aspects of occupational medicine and health care for industrial manpower. Problems of executive health are touched upon, but the emphasis is on preventive care for labor. The approach is straightforward, original, and occasionally highly individualistic.

Chapter I discusses the economic and social framework of occupational medicine. Chapter II describes its evolution in time. Chapter III examines organizations interested in the health needs of employees. Chapter IV is entitled: Management Sets the Policy for Occupational Health. A separate chapter, Chapter V, is devoted to corporate giving for health causes. In Chapter VI labor's influence on medical policy is analyzed. Chapter VII introduces the professional members of the "Humanological" team. In Chapter VIII the author sets forth his views for a positive program of occupational health. A brief Chapter IX describes the seven cycles of life. Chapters X, XI, and XII deal respectively with recruitment, selection and placement, and training of employees. Motivation and promotion are discussed in Chapter XIII, and supervision in Chapters XIV and XV. Retirement is the subject of Chapter XVI.

By way of summary, Chapter XVII develops a "Constructive Mantalent Development Program" while the final Chapter XVIII, which is more in the nature of an appendix, deals with reports.

The presentation is lucid and occasionally discursive. The author has developed a terminology of his own, including such neologisms as mantalent and humanologist. Readers may quarrel with some assertions such as that man is a "tetrahedron" (page 11) or with some aspects of the underlying theory of the business firm, but the analysis is stimulating throughout. Numerous cases are presented and detailed examples and suggestions are worked out.

This book may be recommended not only to practitioners of occupational medicine, but also to the personnel managers and top level executives charged with decisions bearing on employee health.

Martin Beckmann, Ph.D.
Brown University
Providence, R. I.

Yesterday is a cancelled check; tomorrow is a promissory note; today is ready cash—spend it . . . wisely.—Typo Graphic

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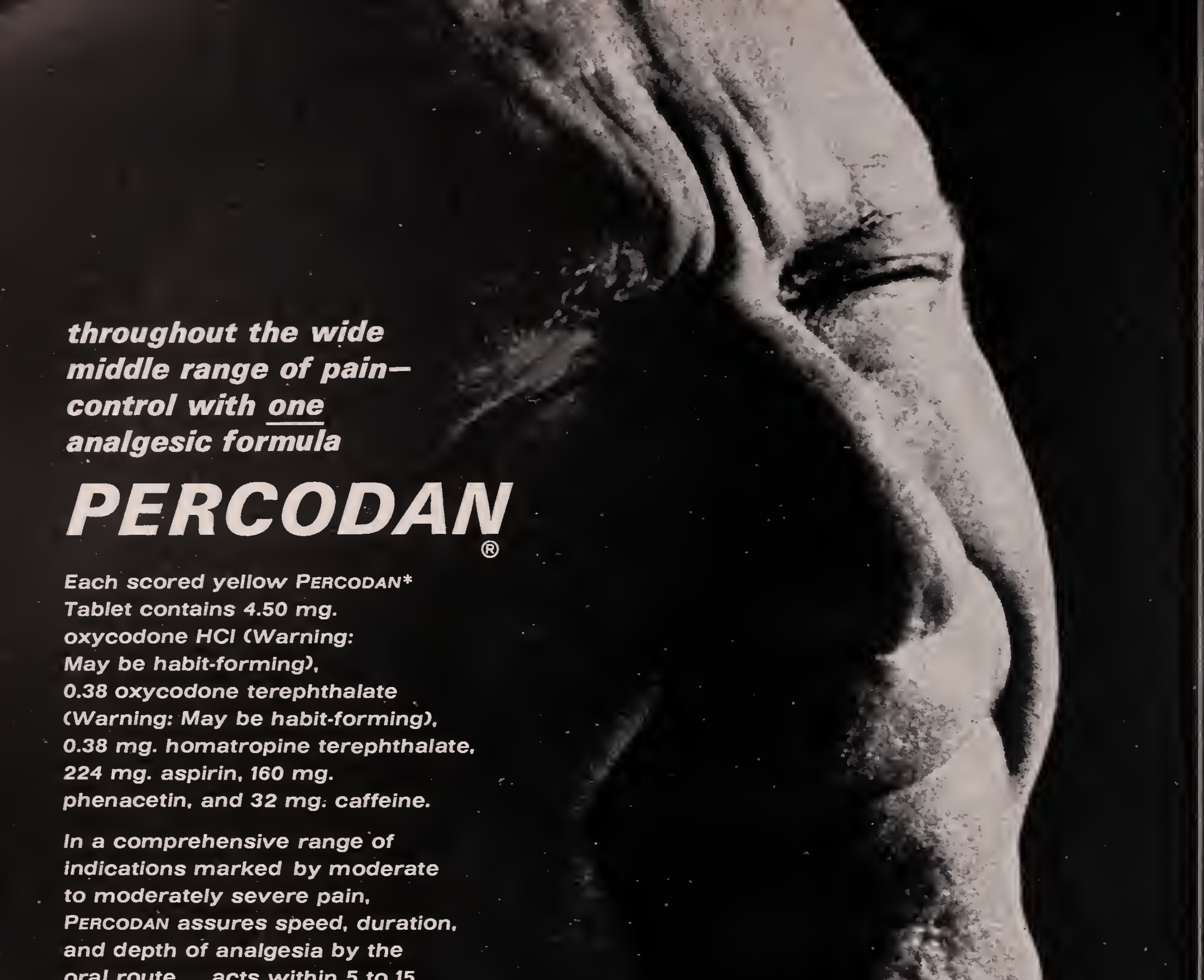
A good neighbor is a fellow who smiles at you over the back fence but doesn't climb over it.—Arthur Baer



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Progress and Personalities in Medicine in Minnesota

S. MARX WHITE, M.D., F.A.C.P.*
Minneapolis, Minnesota

A LITTLE GROUP which developed into the Minnesota Academy of Medicine in 1884 comprised eight physicians and their wives. Primitive as it seems today, records reveal discussion of such subjects as incised wounds, diabetes, the impossibility of excluding germs from a person, and disinfectants for the hands such as carbolic acid and bicarbonate of mercury. Medical consultations were also a matter of interest.

The little group called itself the Unity Club. On October 5, 1887, a meeting in the office of Dr. Charles H. Hunter and Dr. Henry M. Bracken formed the Minnesota Academy of Medicine with 38 charter members from the Twin Cities. At this time, and for more than 25 years thereafter, the standards of medical education and licensure in the United States were very low. By 1910, 100 of the 165 registered schools were little better than diploma mills.

Education Standards Improving

The report of Abraham Flexner in 1910 pertaining to the deplorable state of medical education shook the nation as well as the medical profession out of the existing apathy toward a better standard of medical education and public health. Shortly thereafter the laws on medical licensure were so improved that only 65 legitimate, first class schools survived. Minnesota and California shared the honor of being the first to establish a state board of health. J. N. McCormack, executive officer of the state board of health of Kentucky and traveling organizer for the American Medical Association, stated that Minnesota possessed the best general level of medical practice in the nation. Minnesota's School of Medicine played a significant part in the character of medical practice in the state, despite the fact that its organization was not up to the caliber of many of the eastern medical schools.

Clinical Teachers

Teachers in the clinical departments were for the most part men in private practice who served without pay, giving a few lectures or conducting clinics at the hospitals where they held staff appointments.

Continued

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*Posthumous

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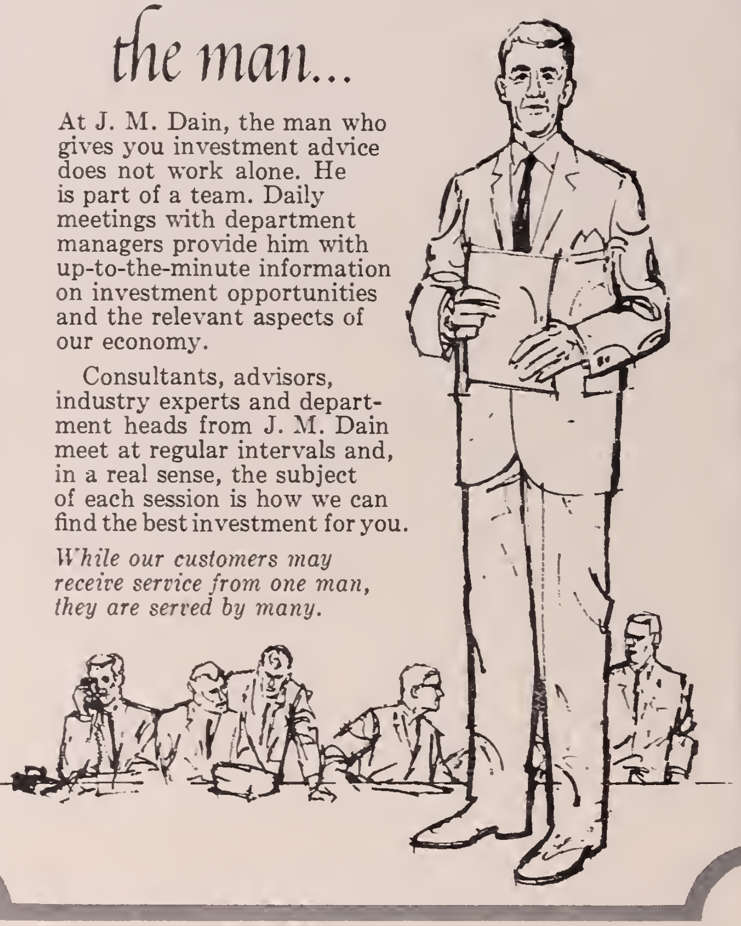

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Until the first world war, the majority of men who planned to teach studied abroad after graduation, chiefly in Germany or Austria.

Milestones of Progress

The programs of the Academy beginning at the turn of the century illustrate how medicine has progressed.

In 1899 H. A. Tomlison stressed the importance of the emunctories.

In 1900, F. F. Wesbrook offered some suggestions of quarantine in diphtheria; and a series of X-ray photographs by Charles A. Erdmann contributed to the study of the anatomy and mechanisms of the wrist joint.

Thrombosis of the coronary arteries with sudden death was described by J. L. Rothrock, having been observed in an autopsy. It was not until more than a decade later that clinical diagnosis began to be made; and it was after the clinical studies of J. B. Herrick and the experimental work of Fred B. Smith of Chicago that the electrocardiograph made possible diagnosis during life.

Surgical treatment of some benign affections of the stomach by William J. Mayo introduced the doctors to gastroenterostomy, a procedure which dominated the surgical treatment for peptic ulcer for a generation.

In 1903 Soren P. Rees mentioned X ray in medical diagnosis, and Arnold Schwyzer, one of the most scholarly surgeons of the region, spoke of bronchoscopy.

In 1904 Walter R. Ramsey discussed preventive inoculation for diphtheria, a scourge of that day.

S. Marx White reported a case of ulcerative angina, presumably caused by the fusiform bacilli and the spirillum of Vincent.

Hemorrhage of the suprarenal capsules in the newborn, with a report of two cases by J. C. Litzenberg, aroused interest when presented later at a meeting of the American Medical Association.

The injection treatment of syphilis by Max P. Vander Horck preceded the discovery of the spirochete by Schaudinn and Hoffmann and the Wasserman reaction in 1906.

In 1905 Archibald MacLaren, emphasizing the failures and mistakes rather than the successes, spoke of the end results of operative treatment for malignancy.

In 1906, a discussion of the physical findings in two cases of pleurisy with effusion was presented by Walter D. Sheldon.

In 1906, Tuberculin as a Diagnostic Agent, by George D. Head.

In 1907, A Resume of Osmotic Pressure and Electrolytic Dissociation, Arnold Schwyzer.

In a presidential address by Arthur J. Gillette on "Why Doctors Are Not More Popular," W. A. Jones was prompted to write an editorial in Northwest Lancet: "Professional men, particularly doctors, frequently have an erroneous conception of their relationship to their fellow men, and are often governed by obsolete views concerning an ethical standard. The writer was astonished to learn that the members of the legislature consider any bill endorsed by the medical profession as unsafe to present to, and difficult to pass, this worthy body. The suspicion is still present, delusional or hallucinatory, that whenever a doctor advocates a reform that will be for the benefit of the public at large, it must result in pecuniary benefit to the physician."

In 1908. The Apparent Relation of High Blood Pressure to Mental Disease, C. Eugene Riggs.

In 1909. The Serum Treatment of Puerperal Sepsis with Report of Six Cases, J. L. Rothrock.

C. Hessel Beckman, an extremely able young man, who became the first nonpolitical superintendent of the Minneapolis General Hospital, and who was later transferred to the Mayo Brothers at Rochester, spoke on the early diagnosis and surgical treatment of cancer.

In 1910. Diagnosis and Treatment of Cerebrospinal Meningitis with Especial Use of Flexner's Serum, S. Marx White.

In 1912. Salvarsan as a Remedy for Syphilis, E. B. Woodard. Prostatectomy and its Sequela, James E. Moore.

In 1916. Narco-local Anesthesia, Robert E. Farr. An Experimental Study of the Effects of Inanition Upon Crowth in Rats. C. M. Jackson. Experimental Pollinosis, Henry L. Ulrich.

In 1920. Study of Some Ossification Centers in the Newborn, Fred L. Adair and R. E. Scammon.

Many subjects of profound interest and significance today received no attention in those first two decades. The conquest of tuberculosis was hardly a dream, though its prevention was considered. The diagnosis was slow, painstaking, and too late. Mass screening with skin reaction came only many years later.

The Electrocardiogram

The period of 1912 to 1918 saw the clinical work of James H. Herrick and the experimental work on dogs by Fred M. Smith of Chicago, which made possible the diagnosis of coronary occlusion in a living patient. The electrocardiograph rapidly became part of the armamentarium of the physician, to be followed by the development and improvement of other apparatus, such as the electroencephalograph, the instrument for electric shock therapy, etc.

The first electrocardiograph brought to the University of Minnesota from England in 1915 by S. Marx White was larger and heavier than an upright piano. The latest model is the size of a suitcase. Endoscopy and other instrumental procedures too numerous to mention have aided diagnosis and provided means of treatment.

Cardiac Surgery

Surgery within the chest was an impossibility until intravenous anesthesia perfected during

World War II by John B. Lundy of the Mayo Clinic. To suggest that a foreign material could be used to repair a defect in the heart wall, or replace a segment of the aorta or other artery, would have been decried. At present the capstone of the electronic engineer's edifice may be the little battery-actuated apparatus supplying the rhythmic stimulus to the man whose own cardiac pacemaker no longer functions.

During the 1940's the use of antibiotics, together with the surgical removal of a tuberculous lung cavity, decreased the incidence of tuberculosis and death therefrom.

Psychiatry

Astounding progress in psychiatry should be mentioned. Since Josef Breuer in 1889 started Sigmund Freud on his work, dynamic studies have replaced descriptive classification and expanded the field enormously.

New Terms

Such terms as enzyme, hormone, and vitamin were coming into use in the laboratory but had as yet no significance to the practicing physician.

Virus Identification

The year 1910 saw R. G. Harrison's demonstration that under suitable conditions bits of living animal tissue could be grown in test tubes. By such means viruses cultured in sufficient amounts are made the basis for vaccines. Since none of our present antibiotics are capable of inhibiting or destroying viruses without damage to the host cell, these vaccines constitute our only defense against them.

The Department of Health

Although the Department of Health of the State of Minnesota was organized in 1872, it was not until 1914 that it began to grow and have influence. Dr. Albert J. Chesley, Director of the Division of Preventable Diseases and later Secretary and Executive Officer of the State Board of Health, made Minnesota one of the leaders in the field. Of his outstanding accomplishments, one needs special mention; he kept the hands and noses of the politicians out of the affairs of public health in Minnesota by prohibiting political connection of any kind and by the strictest economy and honesty in administration.

Paucity of Nonspecific Medications

The physician of today has little conception of the paucity of remedial substances and preventive measures available in the 1900-1910 era. Among those few in general use for some specific effect were quinine, ipecac, the salicylates, digitalis, and the iodides. Of the remaining dozen or so remedies thought to be effective, little or nothing is heard today. Therapy was empiric; the study of effects on animals was in its infancy.

Vaccines

In preventive inoculation, Jenner's smallpox vaccine was effective, but its use was limited by antivaccination propaganda. Pasteur's vaccine against rabies was in use; also his vaccine against anthrax was known.

Early Pioneers

Brief sketches of some men of the period illustrate diversity of background.

Dr. Parks Ritchie

Dr. Parks Ritchie was Dean of the Medical School until 1905. He was professor of obstetrics and a great practitioner, but not qualified as a builder or an educator. He was gentle, lovable, a delightful raconteur.

Dr. Haldor Sneve

A graduate of the College of Medicine of Ohio State University, Dr. Sneve came to Minneapolis in 1890 to practice with Dr. Frederick A. Dansmore, surgeon, and in 1899 became Chief Surgeon of the Great Western Railroad. For several years he gave a course of lectures on gymnastics and hydrotherapy at the Medical School, where in 1911 he became Clinical Professor of Mental and Nervous Diseases, resigning in 1924, along with Dr. C. Eugene Riggs and several other members of the medical faculty who objected to the affiliation of the Medical School with the Mayo Clinic. He was an enthusiastic golfer and an ardent Freudian.

Dr. William A. Jones

Dr. William Jones who earned his M.D. degree at the University of the City of New York in 1881, spent two years as Assistant Physician at the St. Peter State Hospital, then three years in general practice. After studying in Vienna and Berlin, he returned to Minneapolis as a specialist in nervous and mental diseases, and from 1900 on for twenty years he was a clinical professor of those diseases. As president of the State Board of Health he served until 1919; also for many years he was editor of the Northwestern Lancet.

Frank F. Wesbrook

Dr. Wesbrook received his M.D. from Manitoba Medical College in Winnipeg in 1890, studied briefly at McGill University, Montreal, and a year at Rotunda Hospital, Dublin. After several fellowships in pathology abroad, he came to the University of Minnesota as Professor of Pathology and Bacteriology in the fall of 1895; in the spring of 1896 he was appointed bacteriologist to the State Board of Health; in 1906 he became Dean of the Medical School. His contributions up to this time were on rabies, typhoid, and classification of B diphtheriae, the last with Louis B. Wilson and Orianna McDaniel. He had also established the autopsy service in a box stall in the barn behind the palatial residence that was the Minneapolis City Hospital at 6th Street and 5th Avenue.

At Wesbrook's insistence on the need of a University hospital the Medical Alumni Association raised $42,000 and purchased ten acres at the bend of the river south of the campus. The General Alumni Association was at once alerted and bought a large adjacent tract on which Millard Hall, the Institute of Anatomy, and Elliot Hospital with 120 beds were established.

For two years, beginning in 1908, the first services, those in internal medicine and surgery, were located in two very large residences on the north side of Washington Avenue at State Street, with Dr. Charles Lyman Greene of St. Paul and Dr. James E. Moore of Minneapolis in charge.

The Mayo Brothers

Alternating in trips to medical centers in this country and in Europe the Mayo Brothers were able to learn new techniques or study the work of some surgeon of whose skill they had heard. Each consistently required the recognition of the other when some opportunity or award was offered. During the first World War, when W. J. was asked to aid the surgeon general in Washington in selection for the Medical Reserve Corps, he arranged that he and C. H. Mayo should alternate in this service at the national capitol.

In the Clinic, W. J. assumed the principal role in abdominal surgery, and C. H. in surgery of the thyroid and the prostate. As time went on, it was noted that visiting surgeons from all parts of the country, east as well as west and south, became more numerous. As the hospital enlarged, operating suites were expanded and younger surgeons added. Sumptuous provisions were made for visitors to view the work and to confer with Will and Charlie, as everyone called them, between and after operations.

Henry S. Plummer

The first outstanding medical service was developed by Henry S. Plummer, who became a world authority on thyrotoxicosis. E. C. Kendall's crystallization of thyroxin established it as the actual active substance of the thyroid. This was in 1914.

As the Mayo following grew, it became world-wide, especially after World War I. The cataclysm in Europe had caused drastic deterioation in all educational activity there; the centers of medical education stepped almost over night, it seemed, to this country and Eastern Canada. The Mayos' reputation enabled them to draw talent from anywhere they chose, and young men whom they had trained were added in the fields of both medicine and surgery. Dr. Louis B. Wilson had been taken from the University to head their work in pathology but soon took over the direction of their training program.

E. P. Lyon

In 1916 Dean E. P. Lyon had brought Leonard G. Rowntree to the University as full time head of the Department of Medicine. While at Hopkins with Geraghty he had developed the phenol-sulphone-phthalein (PSP) test of kidney function and while at Minnesota had started the first animal experimental work in the Department of Medicine and aided in the development of digitalis lutea and lanata by R. Edwin Morris and myself. As this was the type of activity the Mayos wished to promote in their own group, Dr. Rowntree was invited to go to Rochester.

The Mayo Foundation

The brothers laid aside in a special fund all monies beyond the immediate needs of their families, and this grew by judicious investment. In June, 1913, the Mayo Foundation for Medical

Continued

Education and Research was organized and affiliation with the University of Minnesota was proposed. This it was believed would place the responsibility for control and management in the hands of each generation, furnishing ideal conditions for the perpetuation of the broadly outlined trust and purposes. The amount was $1,500,000.

William J. Mayo had graduated from the Medical School of the University of Michigan in 1882 and while a student there had aided in founding a fraternity, the motto of which was "Not for ourselves alone," a precept inculcated by the father, Dr. William Worrall Mayo, who believed that any man who had a better opportunity than others, greater strength of mind, body, or character, owed something to those who had not been so well provided.

In a letter which W. J. Mayo wrote to the University of Minnesota in 1932 on the occasion of adding another half million dollars to the Foundation, he declared: "The fund which we had built up and which has grown far beyond our expectations has come from the sick, and we believe it ought to return to the sick in the form of advanced medical education which would develop better trained physicians, and to research to reduce the amount of sickness."

The Graduate School

The Graduate School in Medicine at the University has become great, with several million dollars received and spent each year. Together with the affiliated Foundation in Rochester, the Graduate School in Medicine at the University of Minnesota can be said to rival or even surpass many of the schools in the great states farther East.

The first PhD degrees earned in clinical medicine and surgery on the University Campus were three in 1917, the recipients being Golder Lewis McWhorter in surgery, Rood Taylor in Pediatrics, and Henry William Woltman in neurology. Growth in the Graduate School in Medicine has been steady and sound.

Gifts and grants have grown in like manner. The first of record was from Thomas H. Shevlin in 1910 of $10,000, the income from which was to be used for a fellowship in medicine. The year ending June 30, 1962, shows $9,593,284 from gifts, grants and contracts for the support of research, training programs, fellowships, and construction or remodeling of facilities. This is in addition to the regular appropriations.

For physicians' continuation courses a few days to two weeks in length are frequent throughout the year, with attendance from nearly all states in the Union.

Man has learned more in the last thirty to forty years than in all his previous history. Minnesota is notable for its distinguished medical contributions, both past and present.

The Future

I never think of the future. It comes soon enough..—Albert Einstein

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Uncle Sam

Despite what the cartoonists make him look like, Uncle Sam is a gentleman with a very large waste.

Flyer's Rosary

All through the night I prayed my Rosary
On heavenly Beads where only Angels trod.
How can I ever doubt Life's mystery
When first at dawn my humbled soul is awed?
The generous sun gives me so tenderly
Another day—that I may live, for God.—Max Conrad

Meetings And Announcements

MARCH

Department of Otolaryngology, University of Illinois, postgraduate course in laryngology and bronchoesophagology, March 16-28, Chicago. Contact: University of Illinois College of Medicine; 1853 West Polk Street; Chicago.

American College of Surgeons tenth annual meeting in New Orleans, March 16-19, Roosevelt Hotel. Contact: American College of Surgeons; 55 East Erie Street; Chicago.

University of Colorado School of Medicine postgraduate course "Management of Trauma," March 25-27 in Denver, Colorado. Contact: The University in Denver, Colorado.

Mayo Clinic Clinical Reviews, March 16-18 and 23-25 in the Mayo Civic Auditorium; Rochester, Minnesota. Contact: M. G. Brataas; Mayo Clinic; Rochester.

American College of Physicians (Nebraska regional), Lincoln, March 21. Info: Edmond M. Walsh, M.D., 5002 Dodge St., Suite 203, Omaha 2.

APRIL

First Intercontinental Congress of Ophthalmology, April 13-16, Riviera Hotel in Palm Springs. Contact: California College of Medicine, 1721 Griffin Avenue, Los Angeles.

Eighth postgraduate course on fractures and other trauma sponsored by the Chicago Committee on Trauma of the America College of Surgeons, April 22-25, John B. Murphy Memorial Auditorium, Chicago. Contact: Committee, 1791 W. Howard Street; Chicago.

1964 American Industrial Health Conference, April 13-16, Pittsburgh-Hilton Hotel, Pittsburgh, Pa. Contact: American Industrial Health Conference; 55 East Washington St.; Chicago.

American College of Physicians 45th Annual Session, Atlantic City Convention Hall, April 6-10. Contact: College; 4200 Pine Street; Philadelphia, Pa.

University of Colorado Medical Center postgraduate course "Clinical Dermatology" April 23-25, Denver, Colorado. Contact: The University in Denver.

ANNOUNCEMENTS

Applications are now being accepted for the E. V. Allen Memorial Scholarship. Predoctoral and postdoctoral students interested in three months' cardiovascular study at the Mayo Clinic may obtain information from the Minnesota Heart Association, 1821 University Avenue, St. Paul, Minn.

* * *

The next scheduled examination (Part II), oral and clinical, by the American Obstet. & Gyn. Board will be conducted for all candidates at the Edgewater Beach Hotel, Chicago, Illinois by the entire Board, April 27-May 2. Candidates will be sent notice of examination dates.

* * *

University of Minnesota Continuation Medical Courses.

April 3-4	Trauma
April 23-25	Gynecology
May 4-6	Ophthalmology

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Medical Economics

Ways and Means Committee Ends King-Anderson Hearing

Hearings on the King-Anderson bill resumed January 20 before the House Ways and Means Committee.

Meany Stand Questioned

George Meany, President of the AFL-CIO, the principal witness at the opening day of hearings said private insurance and Kerr-Mills cannot meet the health needs of the aged.

In the questioning of Meany, Rep. Thomas Curtis (R., Mo.) challenged Meany's statement that 58 percent of "retired" people do not have health insurance coverage. He noted that the health insurance industry estimates that 60 percent of all aged persons are covered, and asked for further information on the "retired" group singled out by Meany. The AFL-CIO head offered no explanation of the union's 58 percent figure.

The discussion then turned to the cost estimates for King-Anderson. Curtis noted that the union has consistently maintained the cost would be one dollar a month, whereas the bill, itself, calls for $28 from the worker and $28 from the employer a year.

Meany again offered no direct explanation.

King-Anderson Tab High . . . Alger

Rep. Bruce Alger (R., Texas) said a twenty-year-old worker today will have to pay the social security tax for forty-five years with no coverage or protection for himself in order to pay for free medical care for millionaires and others who have paid nothing into social security. The young worker also will have to pay for added health insurance to protect himself in old age because of the limited coverage of King-Anderson in addition to paying for private health insurance during his working years, said Alger.

All of this, Alger continued, for the "privilege" of picking up the tab of a $331 billion deficit in the social security system in forty-five years. This burden on the young worker is unfair and undemocratic, the lawmaker asserted.

Meany said he could not engage in a fruitful discussion.

Rep. James Utt (R., Calif.), referring to charge by Meany that opponents of the bill were engaged in political propaganda, asked Meany if labor did not do the same thing. Meany said the AMA has as much right to be in politics as anyone else.

Javits Committee "Stacked"

Utt noted that Meany had hailed the report of Sen. Jacob K. Javits' study group which recommended a King-Anderson-type bill, and had referred to it as "bipartisan." Utt brought out that eight of the twelve members were "highly partisan" in favor of

Continued

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King-Anderson before they were appointed to the study group. Meany asked Utt if he were implying that Javits had stacked the committee, and Utt said the "answer simply is yes."

Javits Compromise Heard

Sen. Jacob Javits in testimony urged support of his bill calling for a King-Anderson program plus a pooled private insurance plan for medical coverage. Rep. Eugene Keogh (D., N. Y.) questioned the amount of bipartisan support Javits could get, and asked if it wouldn't be wise to take what can be agreed upon as a beginning (King-Anderson) rather than what might be an ultimate goal. The patient has been known to die on the operating table while specialists confer, he said, referring to the different approaches for King-Anderson. The line of Keogh's remarks seemed to indicate the Administration is not prepared, at least at this time, to support the Javits bill as a so-called compromise.

Dentists Oppose Medicare

The American Dental Association presented a powerful statement in opposition to King-Anderson. They said the Association does not believe the problem of the aged is of such dimension as to justify "a vast and irreversible federally administered program providing health services for a large segment of the general population irrespective of need."

"We believe that the health care problems of the aged can and should be solved by less drastic methods" . . . they said.

Flemming Opposes "Hospitals Only" Medicare

Former Health, Education and Welfare Secretary, Arthur S. Flemming spoke for the Javits bill. Committee Chairman Mills questioned Flemming closely, finally getting him to state in an important development that he would oppose the committee's passing of the King-Anderson bill because it only covered hospitals and not medical insurance coverage as well.

Mills questioned Flemming about why the Javits group recommended a public and a private approach.

Flemming said private companies cannot offer adequate policies at a cost the aged could afford. Mills said one part of the Flemming proposal would be voluntary (the medical insurance) and another compulsory (the hospital plan). He asked how this could be accomplished. Flemming said that at the minimum one-third of the aged's health bills would be covered under his program. Mills then asked if Flemming would be against King-Anderson because it contained only the compulsory hospital feature, and Flemming said he is against it.

Then the Ways and Means Committee should not report out a bill dealing only with hospitals such as King-Anderson, Mills asked. Flemming said this was correct.

The second day of hearings started with statements for and against King-Anderson by many lawmakers. Rep. Don Short read the statement of the North Dakota State Medical Association which described how all in the state who need medical care receive it. Short said the state's record was one of "fantastic achievement," especially in view of the fact that it is not one of the richer states.

Rep. Mark Andrews (R., N. Dak.) presented for the record the statement of seventy-six-year-old Peder Ludvig, Valley City, North Dakota, real estate salesman, in opposition to King-Anderson. Ludvig said it would not be fair to saddle the younger workers with an additional tax burden to pay for health services for persons over sixty-five, regardless of need.

Rep. John Dingell (D., Mich.) attacked the Kerr-Mills program as "unamerican" because of the "indignities" of the means test. Under questioning from Rep. Thomas Curtis (R., Mo.), Dingell at one point said old people are "dying like flies" waiting for the states to implement Kerr-Mills.

Rep. Richard Bolling (D., Mo.) was challenged on his statement that King-Anderson would provide an "earned right," and that people with savings are denied benefits under Kerr-Mills. He later conceded that the aged with savings can participate in Kerr-Mills, and admitted that "social insurance" was different than regular insurance.

Continued

Farm Bureau Testifies

The American Farm Bureau Federation said that "increasing the social security tax to provide medical assistance would be burdensome to the self-employed farmer and impose additional controls which he resents."

The Farm Bureau said farmers are "jealous of their independence and are little disposed to spend money on such government programs."

"Farmers want freedom to choose their insurer, and freedom implies diversity," said the Bureau. They added that the trend of proposed "medicare" legislation is "toward conformity and control."

Teamsters Push for all out Medicare

Chief witness for King-Anderson on January 21 was Sidney Zagri, legislative counsel of the Teamsters Union. He said labor-management contracts provide the 1,700,000 members with health insurance protection during their working years, but that this comes to a halt when the member retires. Asked why the union did not try to cover retired members as well, Zagri said the trucking companies could not afford the added cost for "competitive" reasons. The Kerr-Mills philosophy is "an insult to the aged," he said.

The union official attacked the Javits bill. Asked by Rep. Frank Karsten (D., Mo.) whether the AMA's assertion that a majority of the public is opposed to King-Anderson is correct, Zagri replied that 44 percent of the nation's patients are dissatisfied with their physicians, and that medical fees are making physicians increasingly unpopular and causing "something radically wrong" in the doctor-patient relationship. He denied the U. S. has the best medical care in the world.

King-Anderson would Sky Rocket New York Eldercare

William L. Wheeler, Jr., M.D., President of the Medical Society of the State of New York told the committee that if the King-Anderson bill becomes law and goes into effect in 1965, New York State workers will be compelled to pay $3,233,900,000 in social security taxes. "This will be an increase of $341,300,000 over the estimated taxes for 1965 under the present law!"

Mrs. Kenneth Field of Pittsburgh, Pa., a private citizen who has made a study of the state's Kerr-Mills program, said that all of the social service and hospital groups she has talked to have reported successful working of Kerr-Mills. They said hospital patients were pleased with the workings of the program.

"King-Anderson advocates think applying for hospitalization is humiliating to human dignity. In our installment buying age nobody seems to feel he is damaged by the credit manager who probes for every debt, every source of income, every black mark on a man's credit. Why should one single out Kerr-Mills to be humiliated about?" she asked.

Frank Furstenberg, M.D., Baltimore, Md., speaking for Americans for Democratic Action, said King-Anderson doesn't go far enough and that it should cover medical costs, nursing services, social services, and physical and occupational therapy.

New York Mayor Quizzed About Medicare "Popularity"

Under questioning from Rep. Steven Derounian (R., N. Y.), New York Mayor Robert Wagner said Kerr-Mills coverage in New York is extensive compared to other states, but said much of this treatment was available under welfare before Kerr-Mills was passed. The Mayor lead off the third day of testimony.

Derounian said that if King-Anderson is passed, workers eventually will be paying at least $253.50 a year social security tax, and this plus more federal money for hospitals and nursing homes would "cost an awful lot of money borne mainly by the workers."

Wagner replied that labor organizations supported the bill and that they realize they will have to pay for it. Younger people don't mind, he contended, because it means they won't have to take care of their parents' medical costs.

Medicare "Earned Right" Challenged

Rep. Jackson Betts (R., Mich.) pointing to Wagner's testimony that people don't mind paying social security taxes, said he questioned whether small businessmen feel this way.

Rep. Bruce Alger (R., Texas) challenged Wagner's statement that King-Anderson benefits would be an earned right, stating that millions would be eligible for benefits who would not have paid in a cent.

Rep. A. S. Herlong (D., Fla.) called Wagner's attention to the fact that the regular social security system has a means test in that beneficiaries must prove they do not make over $1,700 a year. Wagner spoke of the aged's dislike for charity, Herlong said, yet King-Anderson would be charity for all those who haven't paid for it.

Zalmen Lichtenstein, executive director of the Golden Ring Council of Senior Citizens of New York, said his organization wants doctor bills included in the bills and "a more comprehensive bill would have our full support."

Polls Show Medicare Popularity Lagging

Karl Schlotterbeck, manager of the Economic Security Department of the U. S. Chamber of Commerce, presented a long and detailed argument against King-Anderson, which included the following interesting quotes:

. . . The U. S. Chamber of Commerce spokesman said: "Immediately prior to the Ways and Means hearings on the King-Anderson bill, H. R. 4222, in 1961, a Gallup Poll showed that 67 percent of those questioned of all ages were in favor of medicare.

"Immediately after the defeat of a medicare bill in the Senate in July, 1962, another Gallup Poll was taken and it showed that only 44 percent, or less than a majority of those questioned, favored this kind of program.

"Polls by thirty-four Congressmen in their Congressional Districts in 1963 showed a majority of those replying in each poll opposed to Social Security health care benefits. A majority replied in favor of medicare in only two other Districts.

"Seventeen of those who conducted polls last year on medicare carried out similar surveys during the preceding Congress. In eleven of these Congressional Districts, the majority of replies opposed medicare both two years ago and last year. In each of the six other polls, a majority of those replying endorsed this kind of legislation in 1962, but in the 1963 polls a majority was opposed."

National Medical Association Takes Medicare Stand

Kenneth W. Clement, M.D., President of the National Medical Association, said that legislation to provide hospital insurance for the aged through social security would not harm the doctor-patient relationship and would increase high quality medical care.

The American Podiatry Association submitted a statement that did not support any particular plan, but said that whatever program is approved should provide the aged with podiatric services.

Business Groups Oppose Social Security Medicare

The Commerce and Industry Association of New York said whatever government does in the field of health care should be done through general revenues rather than endanger the social security system. The National Restaurant Association also spoke against King-Anderson.

Doctor Benjamin Spock testifying in favor of King-Anderson said young people have to make financial sacrifices to take care of their parents that could deprive their own children of advantages such as a college education.

The hearings on King-Anderson ended at 1:30 P.M. Friday, January 24. Expectations are that the Ways and Means Committee will vote on the bill in late February or early March after the record of the hearings is completed and printed.

Former Rep. Dale Alford, M.D., (D., Ark.) proposed a "national voluntary medical care plan" under which private health insurance premiums for all ages would be deducted from federal income taxes and where the government would pay the cost of premiums for those unable to afford them. This insurance would provide paid-up coverage at age sixty-five. Doctor Alford said this was his

Continued

own proposal, and urged the committee to consider such an approach.

Rep. Bruce Alger said that he feared that the government's participation in such a program might lead the government to take it over.

Blue Cross Testimony Given

The Blue Cross President, Walter McNerney, did not endorse or oppose specific legislation. He said Blue Cross believes some of the aged "are in a disadvantaged position and require government help in the financing of personal health services."

McNerney said there were some good points to King-Anderson such as establishment of a minimum level of benefits and provisions for consultations with the government by private health groups on operations of the program, such as accreditation of hospitals.

If all older people were placed under a government program and taken out of Blue Cross coverage, McNerney said the result would be only a very small reduction in premiums for the younger aged groups, two or three percent.

He said he was sure Blue Cross could do a good job of administering a national program for the aged.

DISTRICT COURT SUSTAINS MEDICAL BOARD ON TWO LICENSE REVOCATIONS

Dr. J. P. Medelman, Secretary of the Minnesota State Board of Medical Examiners, announced that the District Court of Ramsey County has affirmed the revocation by the Board of the licenses of Drs. Morris Green and Manford B. Dahle.

Dr. Green was originally licensed in 1930. He resided and practiced in California from 1937 until May of 1963, during which time he was twice convicted in California of the crime of abortion and his license to practice medicine in that state was revoked. On his return to Minnesota in 1963, the Minnesota Board conducted a hearing which led to the revocation of Dr. Green's license in Minnesota. He appealed to the District Court of Ramsey County, which on January 9, 1964, affirmed the Board's action.

The license of Dr. Dahle of Olivia, Minnesota, was revoked by the Board on July 13, 1962, after a hearing on eleven charges of unprofessional conduct. He likewise appealed to the District Court of Ramsey County, which on February 19, 1964, affirmed the Board's revocation order.

Dr. Medelman also announced that both cases were handled by Milton H. Altman, newly appointed Special Assistant Attorney General for the Minnesota State Board of Medical Examiners. Mr. Altman is a partner in the Saint Paul law firm of Altman, Geraghty & Mulally and as counsel for the Board will handle all its legal matters.

Where two discourse, if the one's anger rise, the man who lets the contest fall is wise.—Euripides

The Blue Shield

Senior Citizen Contract

(Editor's note: The following article briefly describes Blue Shield's fast-growing Senior Citizen contract. The information is presented in response to a survey contained in Blue Shield's "Progress Report." The survey showed that many doctors were interested in explanatory material on the Blue Shield Senior Citizen contract.)

The Blue Shield Senior Citizen contract, available to persons over the age of 65, has been offered to the public since 1959. The medical-surgical contract is based on Blue Shield's Plan A, which for years has been the most popular contract held by subscribers in the Minnesota Plan.

When the Senior Citizen plan was first marketed, Blue Shield would accept subscribers only during "enrollment periods." Today a person who is over 65 years of age may obtain the contract at any time during the year. Enrollment regulations have been kept to a minimum—the future subscriber need only complete a small application card. He is not required to undergo a physician's examination or submit a statement of health.

The cost of the contract has remained stable since the contract was first put into effect in Minnesota. Today, as before, the price per month per person is $2.95. The cost of the contract makes the Minnesota Senior Citizen Plan one of the least expensive of the many over-65 plans throughout the nation.

In the wake of the political discussions, the Senior Citizen plan has grown in popularity. For example, the number of subscribers holding Senior Citizen contracts from Blue Shield of Minnesota is 20 percent greater in 1963 than in 1962. Moreover, there are 33 percent more people holding Senior Citizen contracts today than there were only two years ago.

The Senior Citizen plan is generally similar in coverage to Blue Shield's Plan A. However, the over-65 plan is not sold to "groups" or as a "family" contract. It does not carry obstetrical benefits. With Plan A, the Senior Citizen plan shares a common level of benefits. Both are paid from Fee Schedule A.

Like Plan A, the Senior Citizen plan offers "service benefits" to low income subscribers. The Minnesota Senior Citizen contract is one of the few throughout the nation that does offer service benefits. The limit for service benefits is $2,400 a year for a subscriber without spouse or family dependents or $3,600 a year for a subscriber with a spouse and family dependents. In addition, the subscriber must meet a test of net worth for service benefits. The individual subscriber must have a net worth of less than $20,000 — or, if he has a spouse, less than $30,000.

Eligibility for service benefits is determined by the total combined annual family income and net worth — and not by the purchase of individual contracts. For example: a subscriber with spouse who holds a single contract must have less than $3,600 a year total combined income. In addition, he must have a net worth of less than $30,000. The combined income would also apply if both the subscriber and his wife held a Senior Citizen contract.

In summary, the Senior Citizen contract provides benefits for the following:

1. In-hospital medical care
2. Generally accepted surgical procedures
3. Diagnostic laboratory and X ray
4. X-ray therapy for malignant and other condi-
5. Related services (anesthesia, endoscopy)
6. Hospital consultations
7. In-hospital electro-shock therapy

The Senior Citizen contract provides benefits up to 120 days of in-hospital medical care. The benefits are paid from Fee Schedule A. Blue Shield will provide benefits usually to only one physician for medical care. However, in the event of serious medical complications with surgical services, Blue Shield may provide medical benefits if the complications are treated by other than the attending physician. Blue Shield may also provide benefits during periods not covered by routine preoperative and postoperative care if the medical complications are treated by the attending physician.

Like other Blue Shield contracts, the Plan offers benefits for virtually every generally accepted surgical procedure. In addition, the contract provides for one hospital consultation per year. A consultation is generally regarded as a service requested by an attending physician in cases where there is a

Continued on Page 347

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History of Medicine

IN WRIGHT COUNTY, Part X

JOHN J. CATLIN, M.D.
Buffalo, Minn.

ROBERT ROSENTHAL, M.D.
St. Paul, Minn.

Editor's Note: This medical history of Wright County commenced in the February 1962 issue of MINNESOTA MEDICINE and continued until December, 1962. For editorial reasons, publication of this history had to be interrupted; however, it is planned to continue its publication until completed.

Patrick (D.P., D.P.H.) O'Hair, located in Waverly in 1881. "Dr. D.P.H. O'Hair, recently of Minneapolis, located in Waverly" states *The Wright County Eagle* of February 17, 1881.

He practiced there as the only physician for awhile, but in 1883 Waverly had three physicians, the other two being Drs. C. Flannigan and W. E. Aubin. He remained in Waverly past the turn of the century. In May, 1882, he opened a drug store; he refitted a storeroom at Fallihee's old stand and called it the "Waverly Drugstore." His card now read "Drugs, Medicines . . . P. O'Hair, M.D., Druggist and Physician. Waverly, Minn."* In March, 1883, he rented George Pannett's building in the east end of town for the purpose of moving his stock of drugs there. In 1885 he built a house.

Late in 1885 he became somewhat of a hero in Waverly.** A man became asphyxiated in a deep well. In a courageous effort he had himself lowered into the well. Dr. O'Hair almost died; he was pulled out in an unconscious state and remained so for some time. In the following year he made the newspaper with the successful removal of a tapeworm 42 feet 10 inches long.† As the years went on the radius of his practice widened, he was called to Delano, Dassel, Watertown, French Lake, Cokato, Buffalo, etc.

Dr. O'Hair was born in Ireland in 1848 and came with his parents to Iowa City, Iowa, in 1849. He received his medical education in Iowa, graduating from the Medical School of the University of Iowa, Iowa City, Iowa in 1880. He supposedly came to Minneapolis in 1880 and was licensed in Minnesota December 28, 1883. He was an active practitioner and is remembered as a kindly old gentleman of the "old school" and was of great service to the people in the surrounding territory. A newspaper item tells that he paid "strict attention to business and was gentlemanly in every respect."‡ He must have been a staunch Democrat as he is particularly remembered by people belonging to that political party. He was a public-

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*The Wright County Eagle, May 19, 1882.
**The Wright County Eagle, October 22, 1885.
†The Wright County Eagle, February 18, 1886.
‡The Wright County Eagle, August 2, 1888.

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spirited man, was greatly interested in government politics and everything that concerned the public. His brother Mike was an attorney in Delano for many years; another brother, John, lived in Morris, and he had a sister, Hanna.

He was a charter member of the Wright County Medical Society when it was reorganized in 1894, and again in 1903.

Dr. Olston of Cokato was called to a shooting victim at Smith Lake in December, 1880.* Another doctor had stated that the shot went through the hip only, but Dr. Olston was able to recognize that the patient had also suffered a perforation of the bowel. Although in critical condition for some time the patient recovered.

He is probably identical with Dr. H. A. Olston who practiced in St. Paul in 1889, a graduate from the College of Physicians and Surgeons, Keokuk, Iowa, in 1874.

Frederick M. Peironnet, practiced in Waverly when the Wright County Medical Society was reorganized under its new name in 1894 and he was a charter member. He was a graduate of the College of Physicians and Surgeons, St. Louis, in 1887 and was licensed in Minnesota in the same year. In 1890 he practiced in Minneapolis and around 1894 and 1895 in Waverly. In the 1920's he was in California. Dr. Peironnet died at Palo Alto, August 20, 1940.

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*The Eagle, December 23, 1880.

To Be Continued Next Month

Blue Shield continued from Page 343

bona fide and urgent need.

In addition, the Senior Citizen contract provides benefits for anesthesia, Isotope and X-ray therapy, electro-shock therapy, diagnostic tests up to $50 per 12 months, X rays up to $50 per 12 months, as well as for a number of special services as enumerated in the Blue Shield Senior Citizen contract.

Not covered by the Senior Citizen medical-surgical contract are hospital or nursing services, medicines or drugs, the services of an intern or resident physician or medical services rendered to other than a hospitalized bed patient, or correction of cosmetic defects. In addition, there is a six months' waiting period for coverage of pre-existing conditions.

A doctor may obtain sample copies of the Senior Citizen contract from the Plan's Professional Relations Department. He may also obtain copies of a brochure which highlights the benefits of the Senior Citizen plan.

The Senior Citizen plan is the only one offered to residents who are over the age of 65. However, it is not the only method used by Blue Shield to provide health protection for the aged.

Other methods:

1. continuation of group coverage for older workers.
2. continuation of group coverage for retired employees and their dependents with part or all of the premium paid by the employer under a formal retirement group.
3. conversion of group coverage to individual policy basis upon retirement.
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President's Letter

Annual Meeting

In the coming month, May, 1964, the Minnesota State Medical Association will hold its Annual Meeting in Rochester, Minnesota. The fact that the meeting is in Rochester in 1964 reminds one that twenty years ago, in 1944, the Minnesota State Medical Association, meeting then in Rochester, devoted much of its deliberations to a consideration of prepayment medical-surgical plans. It was at this time that the House of Delegates approved the endorsement and sponsorship of a prepayment plan, directing legal counsel to initiate appropriate measures to develop a voluntary nonprofit service plan to help the public prepay its medical-surgical costs on a basis consistent with income levels of the patients.

The medical profession faced problems. A small problem was economic; a greater one was political. Most of you not only remember but all of you are still aware of these same problems.

In May 1964, we of the medical profession may take pride in the development of an instrument of twenty years ago which provided a prepayment plan for the public. We should not stand on this one act, however, and praise ourselves for what occurred then. We should look at conditions of 1944, and compare them with conditions of 1964; medically, economically and politically. We should then examine critically the status of our plan and its future, on the basis of experience of the past and the conditions of today and tomorrow.

In 1944, proposals were made to the insurance industry to initiate a program with the assistance of the medical profession. The industry was not sufficiently interested. In a sense, this limited vision caused the Minnesota State Medical Association to organize its own plan to be known as Blue Shield. Since then the insurance industry has noted the success, value and need for such a plan. It has entered the field with such vigor that significant competition exists today in the field of prepayment medical-surgical coverage. The resultant effect, contrary to the best interests of the public, is that the product is now based upon price. There is a watering down of coverage which is sold too greatly upon the basis of price and too little upon the basis of quality.

As the years passed we watched Blue Shield grow into a program of quality. We were pleased but not interested enough to watch over it closely. While this continued, changes became apparent in our everyday practice. Our offices were and are confronted daily with a host of coverages, a host of forms, a host of paper work. We frequently do not know whether our services are covered; whether or not the money will ever be received to pay for the services. These facts are economic. They do not interfere with the quality of medical care rendered. We do not ask a sick person whether or not there will be payment. We provide a uniformly high quality of care, disregarding the economic aspects.

Yet today, faced with quality reduction caused by competition, we find our own Blue Shield plan entering into the competitive field. It disregards the original intent (for the public health) and bows to the dictates of

Continued on Page 464

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The Painful Shoulder

Etiology and Diagnosis

LAWRENCE E. CERINO, M.D.*
PAUL R. LIPSCOMB, M.D.**
Rochester, Minnesota

THE ETIOLOGY of pain in the shoulder presents a challenge to all physicians. It is imperative to remember that specific causes underlie the symptom of "shoulder pain," and all efforts should be directed toward categorizing the causes in terms of a definite diagnosis. Vague and secondary diagnoses like "frozen shoulder" and "bursitis" should spur one to search for possible primary lesions. The treatment of symptoms without first establishing or attempting to establish the etiology is to be condemned. A detailed history and an open mind are paramount.

The causes of shoulder pain are classified as "local" or "distant," depending on the region involved, the shoulder and shoulder girdle being considered as "local" and the spinal column, thorax, and other regions as "distant."

Distant Causes

Cardiac Origin

Cardiac lesions may refer pain to the shoulder through the spinal nerves T1-T4 which supply afferent pain fibers via sympathetic paths to the deep cardiac plexus.[1,2] Typically, this pain, associated with angina pectoris and myocardial infarction, is infraclavicular and on the medial aspect of the left arm. Occasionally, the discomfort may extend to the neck and jaws, or even to the opposite arm. Such referred pain usually is associated with precordial pain, but it may not be.

Disuse of the limbs secondary to myocardial infarction or chronic pain of cardiac etiology may give rise to the complication of periarthritis of the shoulder (frozen shoulder), a painful condition associated with limited motion. In cases in which causes of shoulder pain are obscure, cardiac investigation may be of value.

Diaphragmatic Origin

In the embryo, the diaphragm develops from the neck region and thus its innervation is through cervical spinal nerves, C3, C4, and C5, as the phrenic nerve.[2] Any stimulation of the nerve endings of the superior or inferior surface of the diaphragm may be interpreted as shoulder pain. The cause may center about one of a number of intra-abdominal situations.

---

*Fellow in Orthopedic Surgery
**Section of Orthopedic Surgery
Mayo Clinic and Mayo Foundation

The interscapular discomfort of biliary tract disease is well known to most physicians. Phrenic nerve fibers supply the capsule of the liver, its ligaments, the gall bladder and the parenchyma of the liver itself. Therefore, lesions such as intrahepatic and subdiaphragmatic abcesses masquerade as shoulder pain. The central portion of the diaphragm may be stimulated by a hiatal hernia; esophygeal spasm; free air secondary to laparotomy; a perforated viscus, especially in association with peptic ulcer; or intra-abdominal hemorrhage as seen in ruptured ectopic pregnancy. These and other lesions produce symptoms and signs of intra-abdominal mishap which usually make the diagnosis evident. Yet, in a search for the source of shoulder discomfort, these causes may be forgotten.

Referred diaphragmatic pain is usually felt in the supraclavicular area and the trapezius ridge, but in some cases it may be localized subacromially.[3] Such pain is almost never lateral to the acromium. In general, stiffness and limited shoulder motion would not be expected in association with pain of diaphragmatic origin.

Irritation of the upper surface as well as the under surface of the diaphragm must also be considered as a possible source of shoulder pain. Diaphragmatic pleurisy of pulmonary infarction, atelectasis, or pneumonia, especially after surgical treatment, must be considered when this symptom exists.[3]

Pulmonary Origin

Notorious as a source of shoulder pain is the superior sulcus tumor (Pancoast) which applies pressure by direct extension from the apex of the lung into the brachial plexus or the cervical sympathetic chain in the superior thoracic outlet. Severe shoulder pain may be the first symptom of tumor in the thorax. Further involvement of the brachial plexus produces atrophy, motor weakness, and sensory loss which frequently begins in the hand. Horner's syndrome may also be present on the involved side.

Apical tuberculosis and spontaneous pneumothorax are other causes of shoulder pain.

The diagnosis of these pulmonary lesions is established by clinical evidence of either brachial plexus or cervical sympathetic encroachment or both in association with X-ray changes in the pulmonary apex. Destructive changes in the first rib may coexist with apical malignant disease in the thorax.

Origin in Spinal Column

Shoulder pain is commonly caused by irritation or compression of a nerve root. A herniated cervical disk is not uncommon and often diagnosis is difficult. The usual location of a protruded cervical disk is at C5-C6 and C6-C7. Difficulty in diagnosis arises because results of the neurologic examination and the X-ray findings may be entirely normal. The history often reveals previous "stiff neck" or "cricks" in the neck. Neck and shoulder pain and stiffness are major symptoms; pain in the arm usually is present and extends below the elbow on the lateral aspect of the forearm and often goes into the hand. Pain often awakens the patient from sleep at night. It is aggravated by movement of the neck, coughing and sneezing, and pressure on the top of the skull. Neurologic signs, if present, are muscle atrophy and decreased deep tendon reflexes (decreased biceps jerk if nerve root is at C6, decreased triceps if at C7). Sensory loss is usually slight compared to the subjective symptoms (lesion at C6, paresthesia in the thumb; at C7, paresthesia in the index and middle fingers). Roentgenograms may show formation of osteophytes and narrowing of the intervertebral space, but these findings also may be seen on roentgenograms of asymptomatic patients. In general, examination of the spinal fluid is not helpful.[4] A cervical myelogram will confirm the diagnosis in the presence of suggestive signs and symptoms; yet in most cases a diagnosis is made clinically and treatment is prescribed without a myelogram, unless surgical measures are to be performed.

Cervical osteoarthritis, with its limited motion, especially extension, alteration of symptoms with changes in the weather, and characteristic X-ray findings, also may give rise to compression of nerve roots and its associated signs and symptoms and may be the primary cause of pain in the shoulder.

A tumor in the cervical part of the spinal cord may present with pain focused in the shoulder, but the lesion soon reveals its true identity by more extensive signs and symptoms, that is, by involvement of more than one nerve root. Increase of symptoms to involve other regions such as the entire side of the body or the lower extremity, or the opposite side of the body, are all suggestive. Spinal fluid pressure and protein frequently are increased and the fluid is often xanthochromic. Also, the pain caused by cord tumors is aggravated by the supine position.

Diagnosis of metastatic lesions of the cervical vertebrae or the epidural space giving rise to compression of the nerve root may be impossible prior to roentgenographic evidence of changes.

Ankylosing spondylitis of the cervical portion of the spinal column may cause shoulder pain of cervical origin and becomes evident by involvement of the sacroiliac, apophysial and costovertebral joints, and the paraspinal ligaments, and also by other systemic signs of the disease.[5]

Electromyography may be helpful in recording denervation fibrillation action potentials of abnormal muscle fibers and reveals any neurogenic disturbance in the affected myotome.[6]

Local Causes

Because of the rarity of certain lesions, and because of situations wherein the diagnosis is evident or dependent on culture, laboratory test, or definitive X-ray evidence, we list only the following causes of shoulder pain: infections such as tuberculosis (less than two per cent of affected joints occur in the shoulder), osteomyelitis, septic arthritis, syphilitic arthritis, Reiter's syndrome, hemophiliac arthritis, metabolic conditions including gout and ochronosis, rheumatoid arthritis, hypertrophic arthritis, serum sickness, soft tissue tumors about the shoulder, and bone tumors.

Bone tumors at and about the shoulder can give rise to symptoms of shoulder pain and pathologic fracture. The predilection of metastatic tumors for the upper end of the humerus is well known, especially in the case of hypernephroma. Suffice it to say that tumor must be considered as an etiologic factor in shoulder pain.

Other commoner causes of shoulder pain will be discussed more completely.

Trapezius Myositis

This somewhat vague entity has been described by Seaman[7] as a frequent cause of shoulder pain that is usually mild but may be severe. The pain occurs in the trapezius ridge, but may radiate widely from the shoulder. Pain is aggravated supposedly by any passive motion that stretches the trapezius and by any active motion that utilizes the trapezius.

Etiology

Common causes are poor posture such as that resulting from prolonged work at a desk or from driving for long periods, emotional depression with the head drooped forward, flexion-extension injury, chronic trauma, and nervous tension. Correction of posture, the use of heat locally, and the use of other relaxing agents help many patients.

Compression Syndromes of the Thoracic Outlet

This group of syndromes, including cervical rib, scalenus anticus syndrome, and the costoclavicular syndrome has been blamed for compression of the neurovascular bundle, that is, the subclavian artery and vein and the components of the brachial plexus, as they make their exit through the superior thoracic outlet.

In recent years the existence of such syndromes has been doubted. In the past many patients have been thought to have a thoracic outlet syndrome when, actually, a carpal tunnel syndrome existed. It is probable that such a syndrome is present only when vascular compression exists and this situation is unusual.

Shoulder-Hand Syndrome

Reflex sympathetic dystrophy occurs in association with other lesions — either traumatic lesions of the shoulder such as a fracture or a sprain, or distant lesions such as brain tumors, cervical osteoarthritis, pericarditis, distal lesion of the arm (Raynaud's disease, arterial occlusion, and so forth), or any of a number of other causes.

Self-Perpetuating Cycle

The theory is that the original disability causes an alarm reaction, increasing the sympathetic outflow; this outflow in turn causes pathologic changes in the arm and hand that stimulate further sympathetic outflow, thus establishing a self-perpetuating cycle.[8] According to Friedman and associates[9] this syndrome begins with pain and disability of the shoulder which may be sudden or insidious in onset. Pain and disability of the hand follow. Vasomotor and dystrophic changes soon become manifest. The skin of the hand becomes cold, dry, and thick, and swelling occurs. So-called frozen shoulder and fibrosed hand result. This progression of events may cease at any point. Disuse also undoubtedly contributes to this syndrome.

The symptoms may precede, accompany, or follow the manifestations of the original disability. Psychologic aspects also contribute to the shoulder-hand syndrome; the offending arm may be regarded as an enemy of the body by the patient.[8] In the post-traumatic shoulder-hand syndrome, when pain, tenderness, and discoloration persist, one must always be sure to exclude the presence of unreduced dislocations or an ununited fracture.

Treatment

Blocking of the sympathetic outflow with short-acting anesthetics injected about the stellate ganglion may interrupt the cycle of perpetuation and the diagnosis of sympathetic origin of the discomfort may be established.

Rotator-Cuff Derangement

The tendons of the cuff fuse with the joint capsule and envelop the head of the humerus. The supraspinatous, infraspinatous, and teres minor muscles (the external rotators) insert on the greater tuberosity, while the subscapularis (the internal rotator) inserts on the lesser tuberosity of the humerus. Moseley[10] reported that these muscles act in rotation, serve to hold the head of the humerus in the glenoid fossa, and cause it to ascend and descend in the fossa when the arm is abducted and adducted. The cuff, into which the muscles fuse prior to insertion, is responsible for the fine adjustments of movements in the glenohumeral joint.

Supraspinatous Tendon

The supraspinatous tendon is involved most frequently in cuff tears, which may be partial, that is, they do not extend through the full thickness of the tendon; or they may be complete and extend through the full thickness of the cuff and the joint capsule and usually the floor of the overlying bursa. The severity of rupture varies also; for example, the insertion of the supraspinatous or the subscapularis tendons may be avulsed; the greater part of the cuff may be completely detached from both tuberosities; or the bony tuberosity may be avulsed from the humerus.

The Age Factor

In the young adult, due to the great strength of the tendons, the bone will avulse; in older persons the tendon has undergone degenerative changes which make it susceptible to tearing when subjected to excessive stress. The supraspinatous tendon is the site of frequent friction in its position between the head of the humerus and the acromion. Through the years[11] many sites of microscopic injury are replaced by scar tissue along the tendon.

The typical cuff injury occurs in men more than 50 years of age who have done heavy work in the past. An acute sharp pain or a snap in the shoulder after a fall or a strain marks the onset of the injury. The patient may continue working but is limited because of pain which may extend widely into the arm or scapula.

Symptoms

Roentgenograms do not show evidence of fracture, dislocation, or deposits of calcium. Usually, the pain decreases with rest; but motion, especially abduction and flexion, is greatly limited. Shrugging the shoulder with the trapezius is used to assist in abduction.[10]

A more insidious onset may occur in which pain, spasm, decreased motion, and atrophy that have been low grade in intensity for months suddenly become acute for no apparent reason.

Physical Findings

Physical examination in the presence of a torn cuff reveals a normal range of passive motion;[12] the physician can abduct the arm to 90 degrees without pain, but the patient is unable to maintain this position. If the lesion is extensive, the arm falls to the side — an action known as the "arm drop sign," which confirms the diagnosis.[10] If the lesion is a partial tear, this action is less dramatic. The initiation of abduction, mediated by the supraspinatous, is frequently painful. The cuff should be palpated in all degrees of rotation, and a search should be made for a defect that suggests complete rupture.[11] During the acute stages, examination of the shoulder is often difficult because of the patient's distress. After two to three weeks, atrophy of the supraspinatous and infraspinatous muscles occurs and causes unusual prominence of the spine of the scapula.

On X-ray examination, the head of the humerus is carried high under the acromium by the upward pull of the deltoid muscle, since the injured supraspinatous muscle no longer holds the head in the glenoid fossa.

In cases of tears in the cuff, examination is easier after the injection of a 1-per cent solution of procaine into the insertion of the supraspinatous muscle at the site of maximal tenderness. The injection relieves pain and muscle spasm and restores movement, but abduction against resistance is still impaired. Paralysis of the axillary nerve is excluded by palpating the contracting deltoid muscle. Ruptures of the cuff must always be considered in association with fractures and dislocations of the shoulder.

A partial rupture of the cuff cannot be diagnosed clinically with certainty; however, infiltration of procaine will restore power and range of motion and relieve pain.

Complete tears of the cuff establish communication between the shoulder joint and the overlying subacromial bursa through the rent. This communication is the basis for diagnosis by arthrography, whereby the shoulder joint is needled and contrast media are instilled. If dye in the subacromial bursa connects with the dye in the glenohumeral joint, the cuff is completely ruptured. The subscapular bursa will fill with dye since it normally communicates with the joint, while the subacromial bursa does not. Arthrography will not establish the diagnosis of partial rupture of the cuff.[13]

Bicipital Syndromes

Bicipital tendinitis is a nonspecific inflammatory process caused by chronic trauma and subsequent degenerative changes in an aged tendon. Well-localized tenderness is present in the bicipital groove where the long head of the biceps muscle passes to attach to the supraglenoid tubercle.[14] Pain is aggravated by active use of the biceps and passive stretching of the tendon and muscle.[15]

The onset usually follows severe activity. Relief may be obtained by local injection of procaine solution and hydrocortisone into the tendon. Injection of procaine solution into the glenohumeral joint also may relieve pain, because part of the tendon is intra-articular.

Recurrent Subluxation of the Biceps Tendon

Patients with a dislocating biceps tendon exhibit an abnormal shoulder motion on external rotation which causes a painful, often audible click and is followed by locking of the arm. This locking may be released by reversal of the original motion. On examination, displacement of the tendon is palpable, since the tendon slips out of the groove onto the anterior surface of the lesser tuberosity when the humerus is rotated externally. This may occur because of stretching of the overlying ligamentous capsule by the subscapularis pulling in an opposite direction during repeated forceful movements in external rotation.

Elongation of the biceps tendon may occur secondary to wear and without subluxation. Such laxity may be palpable. Arthrography demonstrates dislocation of the tendon from the groove in case of tears of the bicipital transverse ligament or the synovial reflection. The dye is seen to run down into the arm through the tear in the synovial fold.

Rupture of the Biceps Tendon

Motion of a degenerated tendon in the bicipital groove of the head of the humerus sets the stage for rupture of the biceps tendon. Rupture usually occurs with forceful lifting but may occur spontaneously. Spontaneous occurrence is often associated with previous shoulder discomfort. On rupture of the tendon the patient is suddenly relieved of any prior pain. On flexion the biceps muscle becomes limp and the belly of the contracted muscle is seen to ball up in the arm.

In acute traumatic rupture of a strong tendon subsequent to severe strain, sudden sharp pain may occur accompanied by loss of power and the appearance of a mass over the biceps; hemorrhage occurs and a hematoma forms on the ulnar side of the arm at the elbow. A cuff tear may occur at the same time as the rupture of the biceps tendon.

About half of the ruptured biceps occur in the long tendon; a lesser number occur at the attachment to the glenoid and at the musculotendinous junction; and a few involve the short head, the distal tendon, or the muscle itself.[10]

Calcium Deposits in the Musculotendinous Cuff

Bosworth[16] demonstrated by means of fluoroscopy that almost three per cent of normal people have calcium deposits in the cuff. This figure is probably low because more details can be seen on roentgenograms than by fluoroscopy. Deposits tend to occur bilaterally. More than 50 per cent occur in the supraspinatous tendon, usually laterally, but they may occur in any of the cuff tendons or in any combination. Deposits are noted mainly at sites of degeneration and stress. Normal tendons of healthy patients also appear to contain many asymptomatic calcium deposits. Concentrations of calcium in the serum and urine are normal; calcification of the cuff is not found in patients having hyperparathyroidism, although there may be widespread calcification elsewhere in the body.[17]

Symptoms

Codman[18] showed that calcific deposits in the tendons may last for many years, then gradually migrate into the bursa where they are eliminated by the action of leukocytes. Many deposits are absorbed directly from the tendon. The calcified mass is firm and dense and attached securely to the tendon, but recurrent episodes of acute inflammation tend to soften and loosen the deposit from the tendon.[3,10] This loosening may result from the increased vascularity present at the time of flare-ups of acute inflammation. These attacks cause severe pain in the shoulder and may last for days or weeks. Because of the pain, movements of the shoulder are limited. The patient avoids abduction and sleeping on the involved side. Motion increases as pain decreases. Moseley[10] stated, "Any adult who develops acute pain in the area of the humeral head so that sleep is impossible and the pain unbearable without analgesia, has a calcium deposit until proven otherwise."

During these recurrent flares, a sudden severe episode of pain may occur, indicating extrusion of the calcium into the bursa; then the pain decreases for seven to ten days as the calcium is absorbed from the bursa.[17] Thus, an acute, severe episode in which the intensity of pain differs from previous attacks is probably the result of a rupture of calcium into the bursa and not the development of another episode of acute inflammation.

X-ray Findings

The roentgenographic appearance of pseudopodia in the deposit, round edges secondary to distention, and radiolucency at the borders are all suggestive of imminent rupture.[17] Anteroposterior X-ray views with the arm in internal and external rotation will reveal most deposits, but superior-inferior views are best for subscapularis, infraspinatous, and teres minor deposits.

Bursitis

Subacromial bursitis probably does not exist as a primary lesion but frequently occurs secondarily. Normally the lining of the bursa is thin like peritoneum; but as it becomes irritated and inflamed, it thickens and may distend and form a mechanical obstruction to abduction.[19] Pain is severe with bursitis and may radiate to the neck or into the arm. The slightest motion, especially abduction, aggravates the pain. The patient will avoid lying on that side at night while sleeping. Bursitis may develop secondary to multiple situations, including rupture of the cuff, deposits of calcium, bicipital lesions, arthritis, and fractures. For these reasons "secondary bursitis" is probably a more accurate term. The primary lesion merits chief consideration.

Frozen Shoulder

This confusing entity may result from any one of a group of various lesions. The pathogenesis of the frozen shoulder may originate with pain, restricted motion, or some local lesion such as bicipital tendinitis. If it begins with pain, the pain leads to restricted motion and then to disuse. If it begins with restricted motion — for example, immobilization by a cast — disuse may follow; then degenerative changes develop and finally pain. If it begins with a local lesion, pain occurs, followed by restricted motion, disuse, and degenerative changes. So, multiple interrelated conditions may give rise to the same end result — the frozen shoulder.

Vasospasm

Pain localized in the shoulder or anywhere from the occiput to the wrist and giving rise to protective muscle spasm may in turn produce vasospasm and may alter the autonomic mechanism.[20] Through disuse and dependency, venous return is decreased, the metabolic demand is altered, and passive congestion and relative hypoxia of the tissues result.[6] This hypoxia may then produce signs and symptoms of sensory deficit in the fingers.[20] In differentiation of the pain of the frozen shoulder from that of irritation of cervical nerve roots, it should be remembered that the pain of muscle spasm does not adhere to nerve paths and does not extend beyond the wrist as does pain of neurogenic origin. The deep tendon reflexes of spastic muscles are hyperactive, and the sensory loss is secondary to hypoxia and thus inconsistent and without anatomic pattern.[20] Although the pain accompanying frozen shoulder may simulate that of cervical nerve root compression, it is also true that a cervical lesion can give rise to a frozen shoulder. Therefore, cause and effect must be clearly discerned.

Periarthritic Personality

The chronic pain of a frozen shoulder may also give rise to general psychologic deterioration. The "periarthritic personality," consisting of passive, apathetic, hyperemotional, exaggerated characteristics with a low threshold of pain and hyperactive vasomotor responses may appear in the patient.[21]

Physical Findings

Physical examination of the frozen shoulder reveals limited passive as well as limited active motion in all directions, but especially abduction, external rotation, and flexion. Partial cuff tears, tendinitis, and neuritis do not in themselves produce limited passive motion. In frozen shoulder there is usually some atrophy from disuse, but only minimal, if any, tenderness.[22] Only 20 to 30 per cent of the patients have had a definite injury, like a fall, at the onset; in most patients the condition occurs spontaneously.[23] Roentgenograms of the shoulder usually do not show evidence of any abnormality unless deposits of calcium are present. Arthrography in chronic frozen shoulder reveals a decrease in fluid content at the joint, obliteration of the tear-drop shadow of the biceps tendon, and contraction of the subscapular bursa.[13]

Prognosis

The natural course of the frozen shoulder is self-limited to a period of months to two to three years.[10] Through the course, pain increases gradually to the point of fixation of the shoulder; then the pain decreases and the frozen shoulder gradually begins to "thaw"; and eventually a normal range of joint motion is regained.

Pathologic Changes

The pathologic findings as recorded by McLaughlin[20] are interesting in that 90 per cent of the shoulders examined histologically showed no evidence of inflammation. The joint space was reduced by obliteration of the synovial folds; however, the adhesions were soft and easily separated. As motion was not increased when these alone were released, they were probably a result rather than a cause of frozen shoulder. The bursa was not inflamed — it was only atrophic. The synovia was tight and shrunken about the humeral articular cartilage but peeled off freely; however, no increased mobility resulted with release of this cover. These findings also were thought to be a result rather than a cause of frozen shoulder. The rotator cuff was contracted so that it held the head in tight embrace; the muscle bellies were inelastic and immobile, but histologically normal.[20]

McLaughlin[20] also pointed out the relation of collagen to the frozen shoulder. Most of the cuff is tendinous and thus collagenous; approximately 20 per cent of the muscle bellies are collagenous. This collagen tissue is subject to alteration by changes in water balance related to chronic stress and adrenal stimulation. Loss of water alters collagen so as to decrease its elasticity and cause shrinkage. McLaughlin[20] reasoned that frozen shoulder results because of pain and its associated stress, and adrenal stimulation or stress as a result of the primary lesion.

Many questions remain unanswered in relation to the frozen shoulder. For example, in frozen shoulder-hand syndrome, why is there no "frozen elbow?" What causes the frozen shoulder to "thaw?" What "pops" during manipulation of a frozen shoulder?

Summary

In consideration of the painful shoulder, multiple etiologic factors with similar symptoms and effects on the structure and functional mechanisms of the body may cause confusing clinical pictures. The interrelation of the original lesion and its complicating factors must be realized and evaluated carefully as to cause and effect. An accurate history of the patient and a thorough physical examination will lay the groundwork for accurate diagnosis of the painful shoulder.

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13-23 will appear in the reprints or can be obtained from the author.

IT'S THE LAW

The hospital can be held liable for the negligence of an intern as an employee of the hospital, even though there is no negligence by the hospital in the selection and employment of the intern.

Success is a fraud after all. By the time you're rich enough to sleep late you're so old you always wake up early. — Inland News

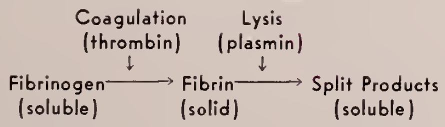
The Pathogenesis of Arterio-Sclerosis*

TAGE ASTRUP, Ph.D.**
Washington, D. C.

THE ETIOLOGY OF atherosclerosis and arteriosclerosis is still obscure. In spite of extensive research and voluminous data we still lack the necessary tools to unlock the mysteries of this disease pattern. During the past years a new concept of the basic processes involved in the pathogenesis of this group of disorders has been slowly developing. Using this concept, it is possible to design new types of experiments for extending our basic knowledge. Perhaps more definitive therapy and, possibly, better prophylaxis can result.

More than a century ago in Vienna Karl von Rokitansky described in detail pathological lesions in the arteries and in the heart, accompanying the disease we call arteriosclerosis.[6,21] Rokitansky demonstrated lesions which he called fibrinous deposits on the arterial intima, which he considered to be a cause of various pathological changes, including intimal hypertrophy, intimal vascularization, calcification, atheroma formation, and weakening of the media with aneurysm formation. Similar deposits of fibrin on the endocardium were described, and he assumed they lead to endocardial thickening and fibrosis, much in the same way as was suggested recently by Penfold.[38]

Rokitansky believed that the fibrinous deposits were produced by an interaction of an exudate released by a local inflammatory process in the vessel wall or in the endocardium, with fibrin forming compounds of blood, by means of a catalytic process. Rokitansky's concepts, arrived at by brilliant intuition, were premature only because they



The dynamic hemostatic balance in the living organism. (From 3).

Fig. 1.

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**Director of Research, The James F. Mitchell Foundation, Institute for Medical Research, Washington 15, D. C.

were impossible to prove or disprove. A century ago the physiological and biochemical background needed for this was nonexistent. With the foundation of cellular pathology by Rudolf Virchow, Rokitansky's ideas were considered obsolete and erroneous, and they soon ceased to form the basis of investigative work and over the years were nearly forgotten. It is of special interest in this context that Rokitansky's suggestion of an interaction of compounds released from the vessel wall with compounds in the blood, leading to formation and deposition of fibrin, was one of the major arguments in Virchow's refusal to accept this idea.

About a century later the British pathologist, J. B. Duguid,[18] studied thrombosed and recanalized coronary arteries. He observed that, at sites where the thrombus had not occluded the whole lumen of the vessel but had apparently formed a mural fibrin deposit on the intimal surface, the resulting pathological process consisted of an intimal hyperplasia leading to intimal proliferation and intimal thickening. Apparently this resembled organization with connective tissue formation of a parietal thrombus. The existence of several layers, clearly separated or overlapping each other, suggested the recurrent formation of fibrin deposits, each followed by fibroblastic proliferation and organization. When deeper layers of thickening occurred, secondary intramural processes appearing as cellular necrosis and lipid deposition were observed. In such processes Duguid saw an etiological factor in the development of an arteriosclerotic lesion. In reaching this conclusion he revived the old suggestion by Rokitansky and laid the foundation for the thrombogenic theory of the pathogenesis of arteriosclerosis. Later Duguid and others have further developed and substantiated this concept.[17,19,20,31,34,44]

Concept of a Dynamic Hemostatic Balance

Since fibrin constitutes the fabric in which fibroblastic proliferation and cellular migration take place after tissue injury, the role of fibrin formation and fibrin dissolution in reparative connective tissue formation has been a classical subject of study ever since such concepts were formulated. About 1900, Leo Loeb[23,30] clearly formulated the concept of a regulation of connective tissue formation during tissue repair as mediated through local clot formation and clot lysis. His concepts, however, were formulated before a clear distinction had been made between thrombin and the thromboplastic agents present in tissues ("tissue coagulins," according to Loeb).

Balance Between Fibrin Formation and Resolution[2,7,12]

Since then our knowledge of the mechanisms of blood coagulation and of fibrinolysis has increased rapidly. It has been possible to formulate a concept of a dynamic hemostatic balance between fibrin formation and fibrin resolution regulating production of reparative connective tissue after tissue injury. It is important to emphasize that we are dealing with a fundamental physiological process participating in the restoration of the integrity of the organism after tissue injury. The cause of the injury is of little significance as long as tissue necrosis is produced, followed by release of thromboplastic activity and fibrinolytic activity from the various tissues.

This concept makes it possible to envisage arteriosclerotic and endocardial lesions as examples of normal tissue repair and connective tissue formation. In this manner a basis for the development of new viewpoints on the etiology and pathogenesis of arteriosclerosis has been formulated. Figure 1 portrays this dynamic hemostatic balance.

The Process of Fibrinolysis

Nolf[36] was the first to connect blood clotting with the process of fibrinolysis. He also assumed that thrombin produced clotting of fibrin as well as the stimulation of fibrinolysis. However, when it was later found that the bulk of fibrinolytic activity in thrombin preparations could be separated from the thrombin, Nolf's concepts became obsolete. They remained so until a fibrinolytic system was described which was activated by a tissue component in a manner very similar to the activation of the blood clotting system by components from tissues.[1] The simultaneous existence of two such systems in the organism, and the activation by their respective activators released from cells after tissue injury, put the inter-relationship on a sound physiological basis. Fundamental to this concept is the assumption that fibrin, formed in the process of blood coagulation as initiated by tissue injury, must again be removed in order to restore normal conditions. Thus, it becomes of utmost importance to delineate the mechanisms by which this hemostatic balance in the body is regulated (Fig. 2).

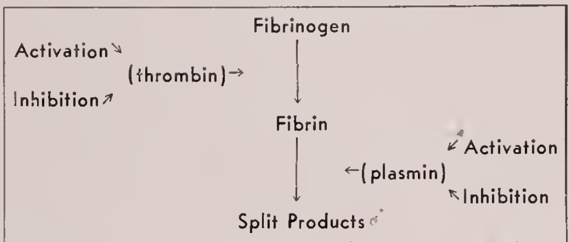
The active agents in this balance are the clotting agent, thrombin, and the blood protease, plasmin (fibrinolysin). The velocity of fibrin formation depends upon the concentration of available thrombin; similarly the velocity of fibrin dissolution depends upon the concentration of available plasmin. The available concentration of the active agents depends upon the effect of activating and inhibiting systems. Thus, if an excessive amount of fibrin was being precipitated at any given moment, this could be due either to an increased activity of the clotting process or to a decreased activity of the fibrinolytic system. In the first case, an increase in the activity of the blood clotting system could be caused either by 1) an acceleration of thrombin production, or by 2) a decrease in the effect of coagulation inhibitors. In the second case, decrease in fibrinolytic activity could be caused by 1) a decrease in plasmin production, or by 2) an increase in inhibitor concentration. It is seen that this system provides the organism with a set of mechanisms by which it can regulate fibrin deposition and tissue repair. This number of variables suggests that locally some system could be more effective than others.

Blood Clotting and Fibrinolysis

In order to better understand the presentation of our experimental findings let us review composition of the systems of blood clotting and fibrinolysis. Two systems are available in the organism for inducing blood coagulation: the extrinsic system based on the release of tissue thromboplastin from injured cells, and the intrinsic system based on the formation, from precursors in the blood, of a powerful blood thromboplastin (Fig. 3).

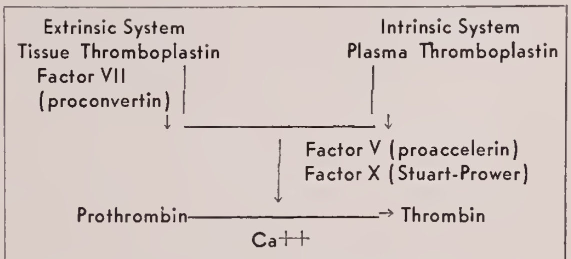
It is known that the effect of plasma thromboplastin is not identical with that of tissue thromboplastin, since the latter requires additional compound (factor VII, or proconvertin SPCA). Figure 3 shows all the accessory factors of the prothrombin system, required in the Quick-test. When this test is normal, it means that the prothrombin system is normal. Formation of plasma thromboplastin requires the compounds shown in Figure 4 — all available in blood plasma.

Initiation of thromboplastin formation in plasma is probably effected by surface activation of the Hageman factor after removal of inhibitory substances aided by disintegration of platelets. By this process a powerful


Fibrinogen
Activation
(thrombin)
Inhibition
Fibrin
Activation
(plasmin)
Inhibition
Split Products

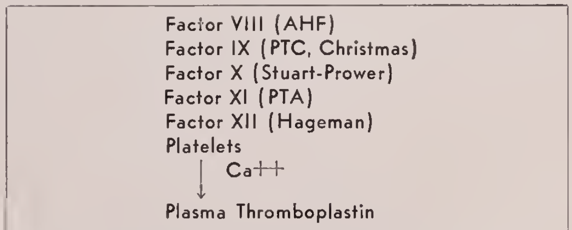
Physiological regulation of balance between fibrin formation and fibrin resolution (From 7).

Fig. 2.


Extrinsic System
Tissue Thromboplastin
Factor VII
(proconvertin)
Intrinsic System
Plasma Thromboplastin
Factor V (proaccelerin)
Factor X (Stuart-Prower)
Prothrombin
Thrombin
Ca++

Extended Fuld-Morawitz scheme of thrombin formation (accessory factors of prothrombin activation).

Fig. 3.


Factor VIII (AHF)
Factor IX (PTC, Christmas)
Factor X (Stuart-Prower)
Factor XI (PTA)
Factor XII (Hageman)
Platelets
Ca++
Plasma Thromboplastin

Components of the plasma thromboplastin system

Fig. 4.

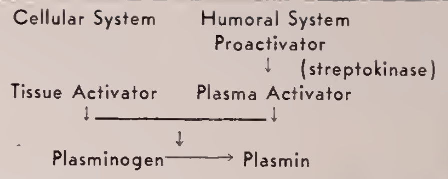
plasma thromboplastin is produced in a short period of time. This system is deficient in persons with diseases belonging to the hemophilioid group. Lack of any of these factors can be demonstrated by various methods, among which the best known are the thromboplastin generation test and the thrombin generation test (in the latter case a normal Quick-test is required, since otherwise thrombin formation does not necessarily reflect plasma thromboplastin formation). Release of tissue thromboplastin and production of plasma thromboplastin each have their own role in the hemostatic process, as examples to be mentioned below will show.

Fibrinolytic Activity

Similarly, there are also two systems for producing fibrinolytic activity (Fig. 5): a humoral system based on the formation of an activator in blood, and a cellular system (incomplete) based on release of activator from tissues. There are many experimental data now to suggest that blood clotting is a process continuously going on in the organism. The rapid turnover rate of the blood clotting components (including fibrinogen and platelets),[35] is one of the most significant observations supporting this suggestion. It is very difficult to explain many observations if mechanisms other than a continuous clotting process are proposed. Not until the fibrinolytic system had been partially elucidated and could be incorporated in the dynamic balance, however, was a background for an integrative concept created. This immediately involves the concept that fibrinolysis also is continuous.

The Hemostatic Balance and the Arterial Wall

Using simple biochemical and physiological evidence in developing the concepts described above, we have been lead to conclusions concerning the etiology and pathogenesis of arteriosclerotic lesions which are similar to those of Rokitansky and Duguid. Our results constitute supporting evidence for the validity of the thrombogenic theory, since our data were obtained in a different manner and from a different background.



The two systems, of cellular or humoral origin, for activating fibrinolysis.

Fig. 5.

Diffusion Process

It is easy to understand why a serious situation occurs if fibrin, after being deposited on the intimal surface in an artery, is not quickly removed again (Fig. 6). The peripheral parts of the wall (adventitia and part of the media) are provided with blood vessels (vasa vasorum) supplying oxygen and nutrients to these layers, and also by further diffusion to other parts of the media. The innermost part of the media and the intima are supplied with nutrients by diffusion from the lumen. When this diffusion process is hampered by the deposition of fibrin on the endothelial surface, a critical zone of decreased nutrition results. If this delayed diffusion of nutrients remains uncorrected for any length of time, necrosis sets in, releasing cellular material and causing an exudative process, followed by weakening of the vessel wall. What are the chances that fibrin will be deposited on the vessel wall? And how quickly can the fibrin be redissolved? These are important questions in the pathogenesis of arterial disease.

First, it is difficult to believe that fibrin would not be deposited on an arterial wall on certain occasions. Fibrinogen and the blood clotting components are abundantly present in the circulating blood. In order to obtain a clearer picture of the fibrin depositing process in arteries we have studied the thromboplastic and fibrinolytic activity of the layers of the arterial wall (Fig. 7).

Thromboplastic Activity of Aorta

Results obtained in studies of human aortas[3,8] show that there is high thromboplastic activity in the intima, high or medium activity in the media, and low activity in adventitia. The opposite is true for the fibrinolytic activity (estimated as plasminogen activator concentration). Here adventitia is high in activity, while media contains only trace or no activity, and intima is inactive.[3,8,32] From these results it is apparent that any lesion of the human aortic intima (e.g., caused by bacterial toxins, stress, etc.) locally can release thromboplastic activity which will produce deposition of fibrin on the site of the injury. This is part of a normal tissue repair process. However, since fibrinolytic activity is lacking in the intima, components released by tissue injury cannot assist in the dissolution of the fibrin deposited. Its resolution depends, in the human, solely on the fibrinolytic agents brought to the deposit by the blood stream. Since a fibrin deposit on the intimal surface will soon become covered by the endothelium, as apparent from studies by Duguid and others, dissolution must be completed before the fibrin layer is "protected" by the endothelial lining.

Experimentally such a situation was demonstrated by Back, Ambrus, Simpson, and Shulman[14] when they administered fibrinolytic agents (plasmin and plasminogen activator) to dogs after producing venous thrombosis. Only when the thrombus was less than three days old could dissolution be accomplished. When the clot was more than three days old it had been covered by the endothelium and was protected against the fibrinolytic agents in the blood. It is important to notice that the incorporation of a fibrin deposit in the vessel wall by overgrowth of the endothelial lining is a rapid process which is completed long before organization of the clot has taken place.

Fibrinolytic Activity of Blood

It is apparent that, in the human organism, an important role in the dissolution of deposited fibrin is played by the fibrinolytic activity in the circulating blood (the humoral system). It is interesting to correlate this with observations recorded by some authors that arteriosclerosis is less frequent in patients with cirrhosis of the liver, since these patients have increased fibrinolytic activity in their blood; thus a lower incidence of myocardial infarction has been reported.[25] In several animal species this is not the case, since the hemostatic systems in their aorta differ from the human system.[9] The results of a comparative investigation of the systems in some common animal species are presented in Figure 8.

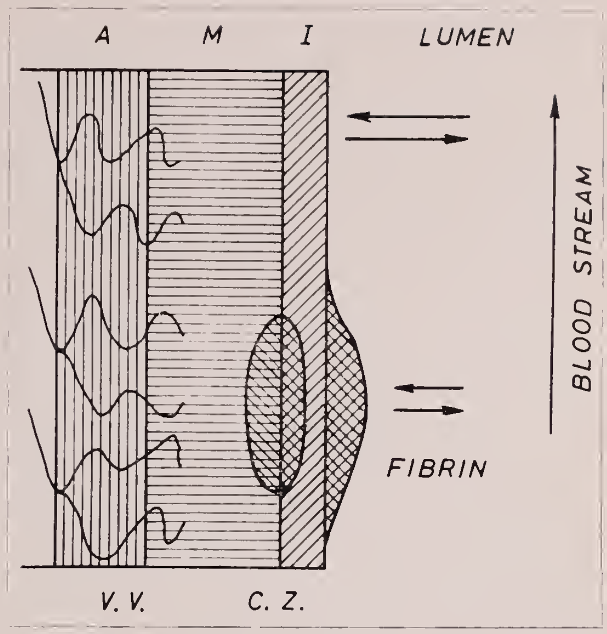
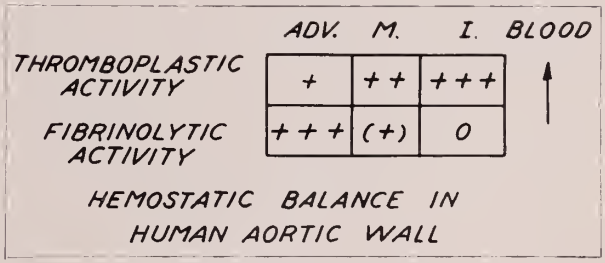


Fig. 6 — Deposition of fibrin on the arterial wall by release of tissue thromboplastin from the intima. A: adventitia (tunica externa); M: tunica media; I: tunica interna; V.V.: vasa vasorum; C.Z.: critical zone of secondary tissue necrosis produced by fibrin deposition (From Astrup[7]).



	ADV.	M.	I.	BLOOD
THROMBOPLASTIC ACTIVITY	+	+ +	+ + +	↑
FIBRINOLYTIC ACTIVITY	+ + +	(+)	0	

HEMOSTATIC BALANCE IN HUMAN AORTIC WALL

Fig. 7 — Hemostatic balance in wall of human aorta. Adv.: adventitia; M: media; I: intima (Astrup[12]).

Hemostatic Variations in Species

In this table the animal species are arranged in the order of increasing thromboplastic activity and decreasing fibrinolytic activity of the intima. The species on the top of the table have a lower tendency to form or retain fibrin on the arterial wall than those at the bottom. It is apparent that animal species vary greatly in their arterial hemostatic systems, suggesting that the process of tissue repair takes a different pattern in different species. It is interesting that the rabbit, a preferred species in studies of reparative connective tissue formation, shows high hemostatic potential in both systems, the thromboplastic activity being high and the fibrinolytic activity low. It is also significant that the dog, an animal preferred in experimental surgical research (especially in vascular surgery), has little or no thromboplastic activity in its arterial wall with moderate fibrinolytic activity. One might wonder to what extent the results of experiments on the vascular system in dogs could possibly be applied to humans. The rat has a blood-clotting inhibitor in its arterial wall, as well as fibrinolytic activity. Recalling the pattern of the hemostatic system in the human aorta (Fig. 7), the human being, when placed in Figure 8, would take positions below the rabbit in the thromboplastic group and in the row with the pig in the fibrinolytic section. This means that man shows a higher tendency than even the rabbit to clot formation, and is nearly as badly off in fibrinolytic activity, though there is considerable fibrinolytic activity in the adventitia. Fortunately, in man there is a high latent fibrinolytic activity in the circulating blood, a possible reason why man has been able to survive so long against such odds. The close similarity between some pathological lesions in the vessels of pig and man has been emphasized by many authors. So far none of the species studied have been found completely identical with man in their vascular hemostatic systems. The human data so far mentioned were obtained in representative and normal (or apparently normal) samples from vessels in normal and arteriosclerotic individuals. No significant differences were observed, though an increase in fibrinolytic activity of the adventitia with age was noticed.

Thromboplastic Activity in Pathologic Intima

Perlick[39] and Kirk[26] recently reported on the thromboplastic activity of arteriosclerotic (atheromatous) parts of the human aorta, which they found generally lower than in normal sections. Kirk noted an especially low thromboplastic activity in ulcerated parts. We have confirmed these observations in a comparative study[11] of apparently normal and atheromatous parts of the aorta from arteriosclerotic individuals (Fig. 9).

It is apparent that the thromboplastic activity of the pathologic intima is only a frac-

Thromboplastic Activity				Fibrinolytic Activity			
Animal	A.	M.	I.	Animal	A.	M.	I.
Rat (15)	Inh.	Inh.		Monkey (6)	151	17	29
Cat (1)	6	0	0	Dog (5)	53	7	7
Dog (5)	0	1	0	Horse (4)	265	23	4
Guinea Pig (20)	3	1		Rat (15)	33	34	
Monkey (6)	8	5	1	Guinea Pig (20)	14	6	
Pig (4)	49	10	4	Pig (4)	533	0	0
Ox (2)	4	25	5	Cat (1)	23	0	0
Horse (4)	19	50	11	Ox (3)	5	0	0
Rabbit (6)	(±)	13	20	Rabbit (6)	0	0	0
Man	1	25	25	Man	300	(0)	(0)

Table comparing hemostatic systems in the aorta of animals. Animal species arranged according to average activity in aortic intima or adjacent coats. Thromboplastic activity in increasing order. Fibrinolytic activity in decreasing order. Average values calculated from individual data. Number of animals indicated in (—). Compiled and arranged from data in [13,16].

Fig. 8.

tion of that in the normal intima of the same individual. Often the activity was higher in the media, a phenomenon much less frequent in our normal samples.[8,11] Apparently there is no support for the general assumption that material from an atheromatous intima has a special enhancing effect on blood coagulation. The high thromboplastic activity seems to be a property of the normal intima.

Fibrinolytic Activity in Pathologic Tissues

The fibrinolytic activity was also estimated (Fig. 10). It is interesting that the fibrinolytic activity of the adventitia is enhanced in the arteriosclerotic samples. This could possibly be related to the pathological process, and is probably similar to the enhanced fibrinolytic activity of the adventitia observed with increasing age. An especially high fibrinolytic activity was found in the adventitia in a sample with medial calcification. It is suggested that this observation is related to the increased vascularization produced as response to the injury for it could be related to the high fibrinolytic activity found in vascularized connective tissue. Examples are the following: meninges of man and animals, adventitia of veins, the capsule of the kidney, the so-called "surgical capsula" of the prostate, and the choroid of the eye.[16,28,29,33,37] It is significant that, also in connective tissue produced in tissue repair, fibrinolytic activity appears in the later stages at the same time as vascularization occurs, as in healed myocardial infarcts and in cirrhosis of the liver.[10,22] Todd, in Duguid's laboratory, has worked out a histological test for fibrinolysis with which he has been able to localize the fibrinolytic activity in tissues.[41] Using this method he demonstrated that fibrinolytic activity is related to the vessels of the venous system. In cirrhotic liver, he demonstrated fibrinolytic activity in the vascularized scar tissue.[42]

Thromboplastic Pattern in Other Vessels

The thromboplastic pattern of the hemostatic system in the aorta is also found, with minor modifications, in other large systemic arteries;[16,27,43] but in veins a lower thromboplastic activity was found. Usually there is also a higher fibrinolytic activity in the venous wall, so that the tendency to deposit and retain fibrin in the vein could be considered less than in the arteries.[16,42] Even the intima of veins was fibrinolytically active. The pulmonary artery, carrying venous blood, showed an intermediate pattern with some fibrinolytic activity in intima and media. Also, in the coronary artery slight fibrinolytic activity was observed in the intima and media. On the other hand, the thromboplastic activity of the coronary intima was higher than in the aorta of the same individual.[16]

Veins

From these data it is apparent that probably the release of thromboplastic material from an injured intima plays a role in inducing clot formation and fibrin deposition. The higher fibrinolytic activity in the venous wall can help to explain why lesions of the

Thromboplastic Activity

Age	Intima Norm.	Media Norm.	Adventitia Norm.	Intima Path.	Media Path.	Adventitia Path.
36	50	25	<1	7	3	<1
38	13	11	3	8	8	2
45	10	10	<1	3	5	<1
58	17	33	4	3	20	<1
64	20	75	33	6	16	16
(same)	—	—	—	4	13	10
70	10	7	<1	1	5	<1

Thromboplastic activity in normal and atheromatous sections of the human aorta. Activities recorded in percentages of a human brain preparation used as reference. From [11].

Fig. 9.

sclerotic type are less frequent in veins (phlebosclerosis) than in arteries.

Vessels in the Hemophiliac

An explanation can now also be given for the appearance of arteriosclerotic lesions in hemophiliac patients, which was believed contradictory to the thrombogenic theory of the pathogenesis of arteriosclerosis.[4] There is no reason to assume that tissue thromboplastin released from the intima in hemophiliac patients should not induce fibrin deposition, since tissue thromboplastin is active on hemophilic blood. An interesting observation in normal organisms is the finding of a nearly complete lack of tissue thromboplastin in human joint tissues (fibrous capsular tissue and synovial membrane from a knee joint).[5] Apparently in places, where tissue thromboplastin is deficient, plasma thromboplastin is required for normal hemostasis. Hence, it can be understood why hemophiliac patients, able to form deposits of fibrin on their arterial intima, nevertheless can bleed into their joints.

Plasma Thromboplastin

We have, in the preceeding, discussed the role of tissue thromboplastin released from an injured intimal surface. However, tissue thromboplastin is not the only blood-clotting agent which can become involved in the pathogenesis of vascular disease. Also plasma thromboplastin can acquire a role, though by way of a different mechanism.

In Figure 6, which shows a diagram of the arterial wall, the appearance of a critical zone of decreased nutrition and oxygenation following parietal deposition of fibrin is explained. It is apparent, and has also been suggested by several investigators, that prevention of blood flow in the nutrient vessels of the vessel wall (vasa vasorum) can produce focal ischemia leading to zonal cellular necrosis. Such a situation would result from the occlusion of the small arteries of the vasa vasorum by thrombosis or by embolization; or it could be produced by vasoconstrictive agents, such as adrenaline or serotonin. It is apparent that since these mechanisms act from the side of the adventitia, while the layers, which normally are supplied with oxygen and nutrients from the lumen (intima), are not primarily involved, the pathological process would develop differently in these cases. The focal zone of necrosis would be more centrally located, involving preferably the media. It is also known from studies on the experimental production of arteriosclerotic lesions that adrenaline produces medial necrosis and affects preferably the muscular arteries, producing lesions of the Mönckeberg-type. Rats respond only with difficulty to diets which in the rabbit produce atheromatosis. They do, however, develop vascular lesions after adrenaline treatment. It is recalled that the arterial intima was highly thromboplastic in the rabbit, while in the rat a clot-inhibitory system was found.[9]

Cellular necrosis following adrenaline treatment will give rise to an inflammatory response with increased permeability and

Fibrinolytic Activity

Age	Intima Norm.	Media Norm.	Adventitia Norm.	Intima Path.	Media Path.	Adventitia Path.
♀ 36	0	0	74	0	traces	384
♂ 38	0	0	180	0	22	740
♂ 45	0	0	138	0	0	360
♂ 58	0	0	154	0	traces	520
♀ 64	0	0	200	0	0	478
(same)	—	—	—	0	0	1188
♀ 70	0	0	324	0	0	984

Fibrinolytic activity in normal and atheromatous sections of the human aorta. Activities recorded in units of plasminogen activator per gram fresh tissue. From[11].

Fig. 10.

accumulation of interstitial fluid. If tissue thromboplastin is present, fibrin formation will soon follow, the focal lesion will be sealed off, and restorative processes will take place. If tissue thromboplastin is lacking, clotting will be slow; but eventually components of the plasma thromboplastin system present in the exudate will become activated and fibrin formation induced. It is reasonable to assume that, in tissues with low content of tissue thromboplastin, the slow activation of the coagulation system will give rise to larger amounts of exudate than in tissues rich in tissue thromboplastin. Consequently, larger amounts of fibrin might be formed, the eventual dissolution of which depends upon the fibrinolytic activity in the injured tissue. An example was seen in the joint tissues. This is the process by which we assume that reparative connective tissue formation is regulated in the organism.

Lipids in Arteriosclerosis

It has perhaps been noticed that so far there has been very little said about the role of lipids in the pathogenesis of arteriosclerosis according to the thrombogenic theory. However, the effects of lipids could easily be incorporated in the thrombogenic theory, without changing its basic structure. It could even be stated there is no contradiction between the concept that lipids play a role in the pathogenesis of arteriosclerosis.

Lipids could become involved in the process in various ways:

1. By causing a shift in the hemostatic balance, e.g., by increasing the activity of the latent clotting system in plasma, or by decreasing the activity of the fibrinolytic system.

2. When incorporated in the fibrin clot during its formation, lipids seem to make the clot more resistant to fibrinolysis.[15] This would tend to decrease diffusion of oxygen and nutrients, thus aggravating the secondary pathological processes (cellular necrosis in the critical zone). Hence a spreading of the process would ensue.

3. Lipids could be produced at the injured site as a result of cell degeneration (fatty degeneration).

4. Lipids could be derived from erythrocytes present in the blood from minute hemorrhages (subintimal bleedings). This source has been stressed, especially by Hartroft.[24]

Viewed in the light of the thrombogenic theory the lipids appear in a multiphasic pattern. They probably play a secondary role as etiological factors, able to aggravate a situation which has already developed, but have little effect if a sufficiently balanced hemostatic system exists. They can be present at an injured site because they have been brought there as part of the process of tissue repair; or they can emerge as a product of the degenerative processes.

It might be appropriate, before concluding, to recall the investigation in 1911 by Ruffer[40] of peripheral arteries of Egyptian mummies from 2000 to 4000 years old. He observed a high degree of arteriosclerosis with extensive calcification. This reminds us that this group of diseases is not solely a product of modern life. It is an old disease, though of greater significance now, when most of the infectious diseases, which lowered the length of life in earlier periods, have been conquered.

Summary

Fundamental observations are presented supporting the thrombogenic theory of the pathogenesis of arteriosclerosis. The physiological background of this theory is given by the concept of a dynamic hemostatic balance in the organism between continuous fibrin formation and continuous fibrin resolution regulating tissue repair and connective tissue formation after tissue injury. It is possible to incorporate the role of lipids in this theory without interfering with its basic structure by assuming that lipids have a secondary role in enhancing and aggravating a pathological process. A discrepancy does not necessarily exist between the thrombogenic theory and the data obtained on the role of lipids.

The thrombogenic theory has opened up new ways of approach to the understanding of the vascular diseases. It is hoped that in following this lead and incorporating the accumulating knowledge about lipids, we might eventually be able to see the conquest of this disease.

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12-44 will appear in reprints or can be obtained from the author.

WHAT'S YOUR DIAGNOSIS?

A 52-year-old farmer was hospitalized because of severe headache associated with nausea and vomiting, which had occurred with increasing frequency in the preceding four weeks.

His medical history included recurring episodes of irregular fast heart beats which had been diagnosed as paroxysmal atrial fibrillation. Five months prior to hospitalization he had been struck on the head by a book end, thrown by a lusty five-year-old grandson. Within a few minutes he had noticed transitory numbness of the right arm and leg, followed almost immediately by unconsciousness for 10 minutes and, on regaining consciousness, persistent left hemiparesis. Anticoagulant therapy was begun four days later and was given continuously without any significant improvement of the left hemiparesis.

The results of physical examination on admission were unremarkable except for the finding of mild left hemiparesis. His blood pressure was 130/90 mm. of mercury and the pulse was 78 and regular. The following laboratory values were obtained: hemoglobin, 9.5 gm.; leukocyte count, 9200 with a differential count showing 68 per cent neutrophils, 16 per cent lymphocytes, 11.5 per cent monocytes, and 4.5 per cent eosinophils; prothrombin time, 36 seconds; and erythrocyte sedimentation rate, 106 mm. in the first hour (Westergren). Roentgenograms of the skull were without evidence of abnormality. The pineal gland was not calcified. The electroencephalogram showed dysrhythmia, grade 1, focal right Sylvian.

What's Your Diagnosis? Turn to page 388.

BERRY'S SIGN

Carcinoma of the Thyroid

This sign may be of significance in carcinoma of the thyroid. When the thyroid is the seat of a malignancy the carotid sheath and its artery become involved in the malignancy and the carotid artery is therefore not palpable lateral to the goiter mass. In a nonmalignant goiter the carotid artery is very often pushed laterally and is therefore palpable.

A chip on the shoulder is too heavy a piece of baggage to carry through life.
— Forbes Epigrams

Significant Rheumatic Fever in Adults

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THE CLASSIC criteria for the diagnosis of rheumatic fever were established principally by observations of the disease in children. Clinicians generally extend these criteria to adult patients, and diagnose rheumatic fever when comparable signs and symptoms are present. This transfer of pediatric criteria to adult medicine has been questioned and may not be entirely valid.

Friedberg[1] stated that a first episode of rheumatic fever in adults over age 25 rarely results in valvular heart disease. The diagnosis of rheumatic fever, according to him, is made too frequently in adults, because criteria which are valid for children may not differentiate it from other adult illnesses.

According to the modified Jones recommendations[2], two major, or one major and two minor criteria are required to diagnose rheumatic fever. Polyarthritis is a major criterion, but when it is the sole major manifestation, other conditions must be considered. Polyarthritis may be the first manifestation of erythema nodosum, ulcerative colitis, polyarteritis, sarcoidosis, drug sensitivity reactions, and systemic lupus erythematosus. Because of this lack of specificity, Friedberg states that in adults, polyarthritis should be considered a major criterion only in the presence of another major manifestation. Chorea, subcutaneous nodules, and erythema marginatum are rare in adults; so carditis is usually required for the diagnosis. The features of carditis are not as specific in adults as they are in children. Pericarditis, congestive heart failure, cardiomegaly, and systolic murmurs are seen in a variety of adult diseases. Friedberg concludes that the only definite evidence of rheumatic carditis in adults is the appearance of a new diastolic murmur.

Thus polyarthritis without another major criterion does not support a diagnosis of rheumatic fever, and prolonged inactivity with indefinite penicillin prophylaxis is probably unnecessary. Friedberg stated that he had never seen valvular heart disease follow an attack of alleged rheumatic fever in an adult over age 25.

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Pader and Elster[3] reported 30 patients, ages 21–59, diagnosed as having acute rheumatic fever. Seven of these were under 25; only 14 cases were thought to be first attacks. Only five of the 30 had "significant murmurs" (not described), and whether any of these were first attacks in patients over 25 was not specified.

Similarly, studies by Slater and Rosenbaum,[4] Hirsch and Flett,[5] and Malpas and Landon[6] included patients under age 25 or were not limited to first attacks.

Cases Studied

This paper is concerned with the appearance of adult rheumatic fever at the Minneapolis Veterans Administration Hospital during the years 1949 to 1960. The diagnosis of rheumatic fever was made in 193 patients. Those who were under age 25 at the time of admission or who had had a previous episode of rheumatic fever were excluded, thus reducing the number of cases to 16.

Clinical Findings

Their ages at the time of admission ranged from 25–41 with a mean of 33, disdistributed as in Table 1 below.

TABLE I

Age	25-30	31-35	36-41
Patients	5	7	4

Upper Respiratory Infection

Ten had a sore throat or upper respiratory infection prior to the development of other symptoms.

Multiple Joint Involvement

All had multiple joint symptoms, and in 12 these were migratory. Arthritis was present in all patients except one, who had only arthralgia. Swelling, redness, or tenderness involving the knee(s) in 12, ankle(s) in six, elbow(s) in five, and wrist(s) in five was present.

Cardiac Findings

Cardiac auscultation revealed murmurs in 13 patients, but most were of questionable significance. These were soft, short, grade 1–2* systolic murmurs at the left sternal border or apex. One patient (Case 13) had an early, high-pitched, blowing, decrescendo, grade 3 diastolic murmur at the left sternal border that had not been heard during hospitalization for tonsillectomy one year previously. Another (Case 3), in whom a murmur was not heard on admission, was later noted to have a low-pitched, rumbling, grade 3, mid-diastolic murmur with presystolic accentuation at the apex.

Skin Manifestations

Subcutaneous nodules diagnosed as erythema nodosum due to sulfonamide sensitivity were seen in one patient (Case 2). In two patients (Cases 4 and 6) an erythematous skin eruption developed during hospitalization. According to the dermatologist both were typical examples of erythema marginatum. Chorea was not seen.

In summary the initial clinical picture in these 16 patients was polyarthritis, with or without other findings suggestive of rheumatic fever.

Laboratory Findings

Electrocardiogram

Electrocardiograms were obtained on all patients. Nine had a P-R interval of 0.22 seconds or more. Six of these became normal during hospitalization and two of the remaining ones were normal at the time of re-examination (September 1960). One patient had complete atrioventricular dissociation, which became normal during hospitalization. Another patient had nonspecific ST segment changes with premature ventricular contractions, still present at the time of followup examination.

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*(on a basis of 6)

Throat Cultures

Throat cultures revealed beta-hemolytic streptococci in five cases, with nonpathogenic bacteria in the others. Anti-Streptolysin O titers were measured in 11 patients. Ten were over 50 Todd units at some time, but only one demonstrated a rising titer (166 to 250). Testing, however, was not done above 333 units and some patients were not serially tested.

Chest X ray

Chest roentgenograms showed no significant cardiac abnormalities, and joint roentgenograms also were normal.

Blood Studies

The erythrocyte sedimentation rate was elevated in all patients from 53–112 mm./hr. (Westergren) at some time during the illness. It seemed to reflect the response of the arthritis to treatment, and had returned to normal at the time of discharge. C-reactive proteins were measured in seven patients and were 3–4+ in four. Other studies including routine and brucella blood cultures, lupus-erythematosus cell preparations, serum uric acids, brucella-agglutinating and blocking antibody titers, latex fixation tests, heterophile titers, and urethral smears were not abnormal.

Re-evaluation

Eight patients were available for re-examination September 1960. Another patient had been seen August 1958, four years after his illness, and was included in this group. Studies consisted of:

1. History that might indicate rheumatic fever prior to hospitalization. (One patient in addition to the 16 reported was deleted from the study because of this.)
2. Other history and physical examination, including cardiac auscultation by two observers (James Brown, former Chief, Cardio-Vascular Section, Minneapolis Veterans Administration Hospital, and the author).
3. Electrocardiogram, chest roentgenogram, erythrocyte sedimentation rate, hemoglobin, and total and differential white blood cell count.

Two months to 11 years elapsed between the acute attack and the follow-up examination, distributed as in Table 2 below.

TABLE 2

Duration (years)	0-1	2-5	6-11
Patients	1	4	4

In no case (except the one that was discarded) was there a prior or interval history of rheumatic fever, arthritis, or illness that could be related to the attack of rheumatic fever. The electrocardiogram showed first degree A-V block, intraventricular conduction defect with left axis deviation, premature ventricular contractions, and a broad, notched P wave (lead II) in one patient each. Other studies did not show significant abnormalities.

Soft, early, grade 1, systolic apical murmurs were heard in two patients, considered functional. One patient (Case 10) had a harsh, grade 2, pan-systolic murmur at the base, transmitted to the neck. Another (Case 3) had a low-pitched, rumbling, grade 3, diastolic murmur at the apex, with a loud first heart sound, opening snap, and diastolic thrill.

Case Histories

Case #4 (see Table 3.)

A 31-year-old postmaster noted the onset of sore throat and posterior nasal discharge in October 1951. He developed pain in the ankles, knees, hands, and spine two months later, which became more severe, and he had a fever of 101° in late January 1952. On admission, January 28, 1952, his temperature was 100.5°, pulse 84/minute, and blood pressure 116/68 mm.Hg. A grade 1, systolic murmur was heard at the second intercostal space, along the left sternal border. The white blood cell count was 12,600/mm.^{3} with 73% neutrophils. Throat culture showed nonpathogenic bacteria. An electrocardiogram revealed a P-R interval of 0.27 seconds, which had returned to normal at the time of discharge. The erythrocyte sedimentation rate was 61 mm./hr. on admission, rose to 77, and was 8 at the time of discharge.

He was treated with penicillin, tetracycline and aspirin. Ten days after admission, an erythematous rash on his back and left arm was noted, consisting of fine, elevated, red lines forming irregular rings which blanched on pressure. The attending staff and the consulting dermatologist considered the rash to be erythema marginatum.

The signs and symptoms cleared, and he was discharged March 14, 1952.

At followup examination August 30, 1960, he was asymptomatic and physical examination and laboratory studies were normal.

Comment:

This patient appears to fulfill Friedberg's criteria for the diagnosis of acute rheumatic fever in an adult. In this instance, eight years later, there was no evidence of residual heart disease.

Case #2 (see Table 3.)

A 30-year-old farmer was admitted May 11, 1950. He had had a severe sore throat five weeks before admission, followed by pain in the knees, wrists, ankles and back, with swelling, redness, and a temperature of 101°. He had been treated with a sulfonamide and tetracyline one week before admission.

On admission his temperature was 100.8°, pulse 85/minute, and blood pressure 130/70 mm.Hg. A grade 2, early, apical, systolic murmur was heard. The liver was palpable, and a 1x2 cm. red, raised nodule was present on the right anterior tibia. The left ankle and wrist were red, swollen, and tender. The white blood cell count was 10,200/mm.^{3} with 82% neutrophils, Anti-Streptolysin O, titer 100 Todd units, and the P-R interval 0.24 seconds. The erythrocyte sedimentation rate was 89 mm./hr. initially, rose to 116, and decreased to 18.

His joint symptoms promptly subsided with aspirin. The nodule on the right leg grew larger and more tender, and similar lesions appeared on both legs. These cleared, and he was discharged November 3, 1950 with diagnoses of acute rheumatic fever, persistent first degree A-V block, and erythema nodosum.

He was readmitted April 20, 1953 with a ten-day history of red, swollen, tender ankles, followed by pain in his elbows and wrists. His temperature was 98.6°, pulse 80/minute, and blood pressure 124/94 mm.Hg. An early, grade 1, basal, systolic murmur and a blowing, grade 1, apical, systolic murmur transmitted to the left axilla were heard. The P-R interval was 0.22 seconds, and the throat culture showed beta-hemolytic streptococci.

He was given sodium salicylate and penicillin. The apical murmur persisted, but the other signs and symptoms promptly receded and he was discharged July 9, 1953.

He was re-examined September 6, 1960. The P-R interval was still 0.22 seconds, but the other laboratory studies and physical examination were normal.

Comment:

This patient is typical of most of the other cases. He had two separate episodes of polyarthritis without other major criteria. Except for the persistent first degree A-V block, no residual cardiac disease was apparent seven years later.

Case #3 (see Table 3.)

A 36-year-old male was admitted April 19, 1956 for severe pain and swelling of the left knee of 10 days duration. There was also involvement of the right knee and hip. Temperature was 97.4°, pulse 68/minute, and blood pressure 110/76 mm.Hg. Tenderness in both knees and right wrist, and a swollen right knee were noted. Cardiac auscultation by two observers disclosed no murmurs. The erythrocyte sedimentation rate was 36 mm./hr. initially, rose to 98, and then decreased to normal. C reactive protein was 4+ initially, and 1+ one week later. He was given penicillin and aspirin with rapid improvement of his symptoms. Diagnosis then was rheumatoid arthritis. Three weeks later he developed left ankle and wrist swelling and again complained of joint pain. A low-pitched, rumbling grade 2, apical mid-diastolic murmur with presystolic accentuation was heard, which diminished as his fever and tachycardia subsided.

He was re-examined November 8, 1960. He was asymptomatic, but had broad, notched P waves in lead II of the electrocardiogram, a diastolic thrill along the left sternal border, a loud first heart sound, and an opening snap of the mitral valve. A low-pitched, rumbling, apical, grade 3 diastolic murmur with presystolic accentuation was heard.

Comment:

This is the only patient in whom valvular heart disease could be demonstrated on follow-up examination, among those who returned. The murmur heard during his acute illness was probably a Carey Coombs murmur.

Discussion

An attempt has been made to answer two questions: 1. Do initial attacks of rheumatic fever occur in adults? 2. If so, can valvular heart disease develop from these attacks? The diagnosis of rheumatic fever by Friedberg's criteria was apparently justified in four patients: two with erythema marginatum, one with a basal, and one with an apical diastolic murmur (Cases 3, 4, 6, 13—Table 3). Two of these patients (Cases 3 and 4) returned for follow-up. One had no apparent disease, the other had asymptomatic mitral stenosis. In the other 12 cases, polyarthritis was the sole major criterion and the diagnosis of rheumatic fever was based on this alone. The absence of significant findings in all seven of the 12 who returned for later examination suggests that rheumatic fever should not be diagnosed in these cases.

Some patients could not be located for follow-up examination, including two of the four in whom the diagnosis of rheumatic fever was confirmed. There were no female patients in this series.

Many cases of rheumatic heart disease have no history of acute rheumatic fever. Similarly an apparent initial episode of rheumatic fever in an adult may be a recur-

TABLE 3
Clinical and Laboratory Data on Patients with Acute Rheumatic Fever

#	Age	Year	History	Heart	Joints	Skin	ECG	Throat Culture	ASO	ESR	C React.	Follow-Up Studies		
												Heart	ECG	ESR
1.	34	1951	migratory arthritis	grade I, sys., left sternal border	swollen, tender ankles, left knee	normal	normal	Strep vir	—	85	—	—	—	—
2.	30	1950	sore throat mig. arth*	grade 2, sys., apex	swollen, red, tend left ankle, wrist	erythema nodosum	I°AV block	normal	100	89	—			
	33	1953	arthritis	grade I, sys., base & apex	normal	normal	I°AV block	B Strep	—	—	—	normal	I°AV block	29
3.	36	1956	arthritis	grade 3 dias., apex, I mo. later	swollen, tender knees, right wrist	normal	normal	normal	50	98	4+	grade 3 dias., apex	P Mitrale	12
4.	31	1952	sore throat arthralgia	grade I, sys., base	normal	erythema marginatum	I°AV block	non-hem Strep	—	77	—	normal	normal	6
5.	26	1958	migratory arthralgia	grade I, sys., apex	swollen, red elbows, right knee	normal	I°AV block	B Strep	166-125	97	3+	—	—	—
6.	34	1951	sore throat mig. arth*	grade 2, sys., apex	swollen, tender knees	erythema marginatum	normal	—	—	96	—	—	—	—
7.	39	1951	sore throat mig. arth**	grade I, sys., apex	swollen, red, tend knees, elbows	normal	I°AV block	—	—	97	—	—	—	—
8.	25	1949	sore throat arthritis	grade 2, sys., apex	tender knees	normal	I°AV block	—	—	98	—	—	—	—
9.	32	1954	sore throat arthritis	normal	swollen, red knees	normal	I°AV block	Strep vir	333-250	53	—	normal	normal	4
10.	41	1960	sore throat mig. arth**	grade I, sys., base	swollen, red, tend knees, ankles	normal	I°AV block	normal	over 333	112	2+	grade 2 sys., base	normal	29
11.	35	1960	sore throat mig. arth*	grade 2, sys., base	swollen, tender knees, ankles, wrists, elbows	normal	normal	B Strep	50+	92	3+	—	—	—
12.	39	1955	sore throat mig. arth*	normal	swollen, red, tend elbows, wrists, right knee	normal	3°AV block	normal	333	98	4+	normal	left axis dev., intraventr cond defect	23
13.	28	1949	migratory arthralgia	grade 3, dias. left sternal border	swollen, red left knee, elbow	normal	I°AV block	normal	333	89	normal	—	—	—
14.	31	1958	migratory arthritis	grade 2, sys., apex	red, tender ankles	normal	I°AV block	B Strep	125	111	1+	grade I sys., apex	PVC's	22
15.	32	1954	sore throat mig. arth*	grade I, sys., apex	swollen right ankle	normal	PVC's	B Strep	125	70	—	grade I sys., apex	PVC's	—
16.	30	1956	migratory arthritis	grade I, sys., apex	swollen, tender r. knee, left wrist	normal	normal	Strep vir	166-250	55	2+	normal	normal	28

*Arthritis
**Arthralgia

rence rather than a first attack. This is crucial to the problem of whether adult rheumatic fever results in rheumatic heart disease, since valvular lesions following an attack of rheumatic fever in an adult, might be due instead to an unrecognized attack during childhood.

This study supports Friedberg's conclusion that significant rheumatic fever is uncommon in adults. Cases where the diagnosis was based on polyarthritis were not followed by rheumatic heart disease. Since rheumatic fever implies that progressive heart disease may follow, a better label for these patients might be "poststreptococcal polyarthritis," as Friedberg suggested.

Summary

The diagnosis of rheumatic fever was evaluated in 193 male patients hospitalized at the Minneapolis Veterans Administration

Hospital from 1949–1960. Of these, only 16 were over age 25 and had no previous history of rheumatic fever. Four of the 16 had major criteria in addition to polyarthritis. Two of these four patients were examined four and eight years later; one had rheumatic heart disease and the other did not. Polyarthritis in adults without another major criterion is not considered sufficient for the diagnosis of rheumatic fever, and later examinations of such patients failed to reveal rheumatic heart disease. The diagnosis of rheumatic fever, which implies future heart disease and the need for restricted activity and penicillin prophylaxis, may not be justified in such patients.

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PHENYLKETONURIA SYNDROME

Phenylketonuria is an inborn error of metabolism and is thought to be found in approximately 1% of institutionalized mental defectives. It is relatively higher in people of European stock. It is thought to be inherited by a simple autosomal recessive gene. One in 70 of the general population is thought to be a carrier of the disease though the incidence in the general population is 1 in 20,000.

In the untreated patient, the infant is born normally but begins to show mental retardation at about three or four months of age. The infant loses interest in surroundings and development is slowed down or arrested until the age of 3.

The phenylketonuric child is usually fairly well developed physically and may have no diagnostic criteria other than the characteristic musty odor. There is usually retardation in sitting and walking and the child may never learn to walk or talk. Most of the children are blonder than the parents. About 80 percent show electroencephalogram changes.

A drop of 10 percent ferric chloride placed on the baby's wet diaper produces a blue-green to gray-green color immediately, but the color fades rapidly.

Dietary treatment must be started in the first few months of life in order to prevent mental deficiency. No benefit can be obtained after the age of three.

Durham—Encyclopedia of Medical Syndromes
Haeber Inc. New York.

ANSWER TO WHAT'S YOUR DIAGNOSIS

(From page 382)

On the patient's hospitalization, the use of anticoagulants was stopped. The angiographic films showed a large avascular area overlying the right cerebral hemisphere. A large right subdural hematoma was evacuated. No other specific abnormality was identified to account for the anemia or high sedimentation rate.

In a democracy, when people aren't sure what they want, they vote for something different from what they have. — Banking

Ureteral Injuries

in Pelvic Surgery for Benign Lesions[**]

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WHEN URETERAL injuries that occur in pelvic surgery for benign lesions are considered, three important questions should be answered: How often do such injuries occur, why do they occur, and what should the surgeon do when such a complication is discovered during an operation? A statement that these injuries *should* not occur does not help; for they do occur, although, as larger series of cases are reported, the incidence seems to be decreasing.

Incidence of Ureteral Injuries

Hofmeister and Wolfgram[1] recently studied the spatial relationship of the ureter in the course of which they noted 1500 vaginal hysterectomies without known damage to a single ureter. Everett and Mattingly[2] from Johns Hopkins Hospital reported 114 injuries to the urinary tract (0.7 per cent) in 15,000 vaginal and abdominal operations. Mengert and Stoltz,[3] in 1945, mentioned 1925 abdominal hysterectomies with 10 known ureteral injuries (0.5 per cent). Our data are incomplete because of difficulty in a retrospective study of identifying those cases in which injuries may have occurred. In the last 10 years, my colleagues and I have known of at least four injuries to the ureter that occurred during vaginal hysterectomies: one ureteral fistula developed; two ureters were damaged — the damage was recognized and repaired during operation; and one ureter was treated conservatively.

According to Abbott and Higgins,[4] the incidence of ureteral injuries is highest in abdominal hysterectomies. Of 48 such injuries in women, 35 occurred after abdominal hysterectomies and only two during vaginal operations. In reviewing the records of abdominal hysterectomies in the last 10 years at the Mayo Clinic, I could find only two recorded instances in which the ureter was inadvertently damaged. My figures are probably inexact, as damage that required only stitching or observation is not cross-indexed in the files at the Mayo Clinic. Therefore, even allowing for my figures on benign lesions being incomplete, the overall incidence of ureteral injury is fairly minimal.

When a ureter is ligated suddenly and completely and the kidney is noninfected, the kidney may atrophy without symptoms. Unless a subsequent urogram or a postmortem examination reveals the nonfunctioning kidney, the surgical injury may never be recognized. A so-called autonephrectomy has been accomplished. Freda and Tacchi,[5] in a study of patients on their fifth postoperative day, found two with ligated ureters in a group of 204 who had had abdominal hysterectomies and none with injuries in a group of 112 who had had vaginal hysterectomies. Since these studies are expensive and time-consuming, they cannot be done routinely. Furthermore, unless preoperative urograms are made whenever such a study is undertaken, no one would know the real incidence of injury. Nevertheless, ureteral injuries are accepted as a hazard in gynecologic operations.

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[**] Read at the meeting of the New York Gynecological Society, Inc., New York, New York, June 26, 1963.

Etiology of Ureteral Damage

The second question is why do they occur? A corollary to this question is related to the location of the injury. The ureter is an anatomically constant structure through the female pelvis; generally, there is one on each side, although an occasional patient may have a duplication. Masson,[6] after 35 years of busy surgical practice at the Mayo Clinic, often remarked that the only abnormally situated ureters that he had encountered were in the first 20 patients on whom he operated.

Extensive Endometriosis

An abdominal pelvic operation, when complicated by extensive endometriosis or pelvic inflammatory disease, is most likely to result in ureteral damage. In 1960, I removed an adenomyoma that involved the sigmoid, cul-de-sac, and a posterior vaginal fornix which had caused considerable difficulty in defecation as well as marked dyspareunia. Excision of the adenomyoma required resection of 9 cm. of rectosigmoid and a portion of the vaginal fornix. As the lesion was mobilized, I found that a troublesome, aberrant bleeding vessel was actually the left uterine artery, beneath which was a 2-cm. segment of left ureter that was pulled practically to the midpelvis and was removed with the adenomyoma. Once the problem was identified, a primary ureteroureteral anastomosis was carried out, and the patient had an uncomplicated convalescence.

Poor Exposure

Most ureteral damage occurs low in the pelvis near the uterine arteries. A number of factors contribute to this. Exposure may be poor because of inadequate incision, difficult anesthesia, or obesity. Cleavage planes may be obliterated by pelvic disease, and scarring and fibrosis may make excision of tissue possible only by sharp dissection. Bleeding deep in the pelvis beneath the ureters or in the obturator fossa can be troublesome, and the speed necessary in attempting control of active bleeding probably accounts for many surgical complications. Blind clamping is the most dangerous method of attempting to control bleeding. Pack the pelvis, if necessary, wash your hands, then carefully remove the packs, observe the bleeding vessels, and pick them up. If stick ties are necessary, identify and expose the ureter to keep it out of the way. In their training, gynecologists seem to have been taught that the ureter is sacred and not to be seen, touched, or exposed. For years, my colleagues and I have considered the ureter a structure that is anatomically identifiable; therefore, we can and do identify it during all pelvic operations; if there is any question of ligatures or clamps being near the ureter, the ureter should be promptly dissected out on its course through the pelvis. Preoperative catheterization is time-consuming and unnecessary. It gives a false sense of security and, in addition, places a hard tube inside the ureter against which the ureteral walls may be crushed by other instruments.

Ligation of Ligaments

The ureter is likely to be damaged in two additional situations. When the infundibular pelvic vessels are ligated or are being extraperitonealized, the ureter crossing the iliac artery is immediately adjacent to the vessels and can be inadvertently included in a ligature. Also when a clamp is placed on the cardinal ligament during vaginal hysterectomy, the ureter may be damaged because of its proximity (Fig. 1). My colleagues and I always check for the ureter just before closing the jaws of the clamp on the cardinal ligament; in approximately 3000 vaginal hysterectomies, I have only twice found the ureter in the clamp on this checking — both times during the same week. Recently, a ureter that was crushed by a clamp was recognized and released immediately. A catheter splint was then placed in the ureter, and no harm resulted. A more extensive and serious injury in 1961 necessitated resection and end-to-end anastomosis of the ureter during the course of a vaginal hysterectomy. Avoidance of injury to the ureter, of course, is best and depends on the exact knowledge of where it should be, the closeness of the instruments to it at any given time, plus the surgeon's taking the precaution of identifying and if necessary exposing it at each important step in all pelvic operations.

Management of Ureteral Repair

The management of ureteral injuries assumes damage to a ureter, and, therefore, the single most important consideration is the recognition of that fact. For if recognized and treated, most injuries will heal readily and well. Weaver[7] gives an excellent but short review of some of the principles of ureteral surgery and emphasizes two points in particular: (1) the ability of the ureter to regenerate large defects when only a strip containing all elements remains, and (2) the inability of the ureter to withstand stretching. The latter means that suture lines should be made with a minimum of sutures and without tension.

Ureteral Splint

Ureteral splints are indicated in damaged ureters and, when utilized, they should remain in place two to three weeks. Any splint, however, should be small enough not to stretch or distend the ureteral walls.

Soft Rubber Drain

Of even greater importance is the placing of soft rubber drains in the region of any ureteral anastomosis. Tissues of the urinary tract will tolerate damage and loss of continuity of portions of the wall but not stagnant extravasated urine about them. Since infection, fibrosis, and strictures may result in the loss of a kidney, adequate drainage should be established. The drains should remain in place seven to 10 days or until a tract has formed that will assure free urinary drainage.

The blood supply to the ureter is variable, but the vessels run parallel to the ureter, and, the less the adventitial coat of the ureter is disturbed, the more likely it is to regenerate and heal quickly. Even a thickened, enlarged, infected ureter is capable of regeneration and does not necessarily indicate nephrectomy.

When Crushed

If it has been crushed in a clamp or has a ligature tied around it, the ureter should be

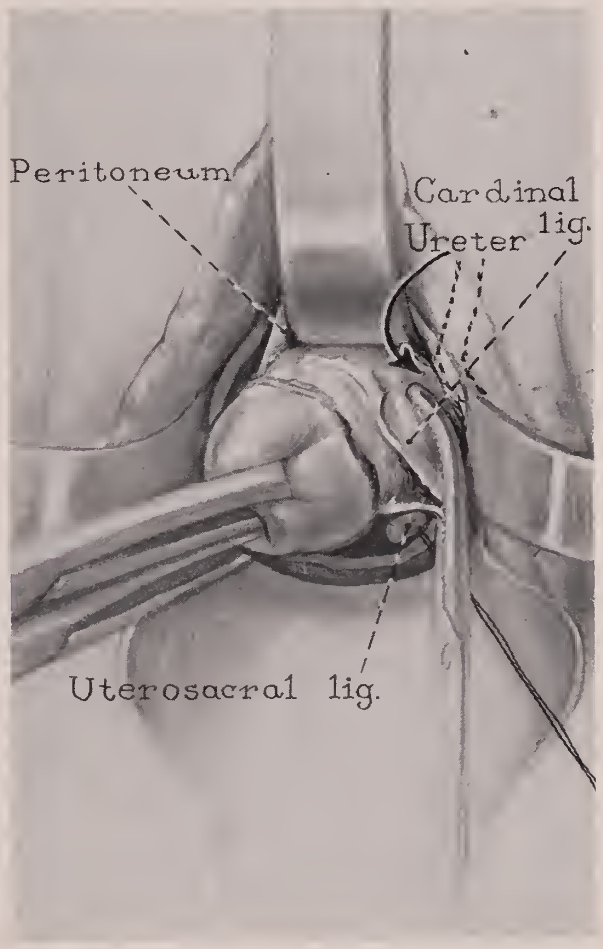

Fig. 1 — Position of ureter when the cardinal ligament is clamped during vaginal hysterectomy. (From Pratt, J. H.: Technique of Vaginal Hysterectomy. Clin Obstet Gynec 2: 1125, 1959. By permission of the publisher, Paul B. Hoeber, Inc.)

freed as soon as possible. A small splinting catheter should be placed past the obstruction to the kidney, and the patient should be given antibiotics and treated conservatively. Primary resection of such an area is advocated by some surgeons and is indicated when there has been extensive destruction of tissue.

Ureteroureterostomy

When interruption of the ureter has been complete, primary end-to-end anastomosis is the procedure of choice. Any method of direct or oblique end-to-end anastomosis, with or without everting sutures, may be used, and an intraureteral splint that does not disturb or stretch the ureteral wall is a necessity. Webb and co-workers[8] reported a particularly refined method of anastomosis. For their anastomosis, which must be without tension, they utilized one row of fine catgut (not silk), with perhaps an extra one or two sutures in the adjacent tissues to relieve any strain. They then drained the area with a soft rubber drain. Weinberg and co-workers[9] added a linear incision in the ureter above the anastomosis to slow up peristalsis for several days.

Ureteroneocystostomy

If the defect is so low in the pelvis that ureteroureterostomy cannot be performed for repair, ureteroneocystostomy should be done (Fig. 2). Numerous methods of bridging defects include: (1) freeing the bladder from the symphysis to allow it to reach practically to the bifurcation of the iliac vessels, (2) forming a tube of bladder wall to extend the bladder cephalad, or (3) making a simple curved incision in the dome of the bladder and closing it at right angles to allow the bladder to reach the ureter. A simple fish-mouth implantation with two to three supporting sutures is probably the quickest and easiest method of implantation, although urinary reflux may occur. Oblique tunnels in the bladder wall or the formation of nipples of the ends of the ureter all have their advocates. From the number of methods available to the surgeon, one must conclude that no method is outstandingly better than any other.

The Ileum Conduit

If the ureteral defect is so large that it cannot be bridged by mobilizing the bladder, tissue from the ileum is the best for use in a conduit, although tissue from the sigmoid, Fallopian tubes, skin, arteries, and veins have all been utilized. A mucosa-to-mucosa ureteroileostomy plus an ileocystostomy functions well and has stood the test of time. Even though the lesion is benign, when the condition of the patient is poor, skin ureterostomies are quick and easy, and reconstruction operation can be done later when the patient is in better condition.

Comments

At the meeting of the Central Association of Obstetrics and Gynecology in 1959, Kelso and Funnell[10] presented the outline of a plan for the care of urinary tract injuries, which is an excellent summary. The cardinal principle, however, is still one of prophylaxis — namely, it is easier to avoid trouble than cope with it. Once a ureter has been damaged, the pelvic surgeon should know and follow basic principles as to the care of the damaged ureter and the various methods for remedying the injury. Recognition of the trouble is paramount, and, since the urinary tract will do its best to regenerate, preservation of renal function with re-establishment of the continuity of the urinary tract should be attempted.

When the injury is not evident at the time

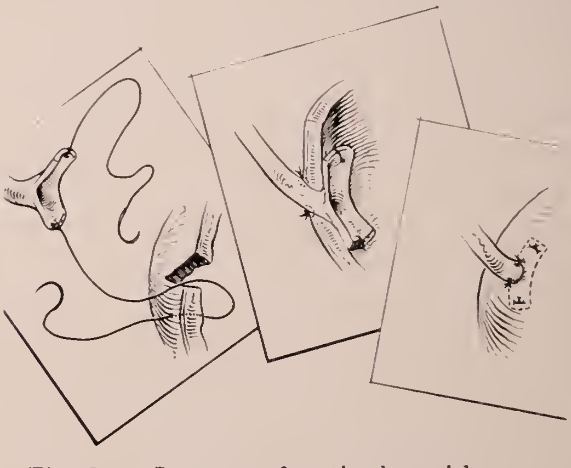

Fig. 2 — Sequence of a simple, quick, easy ureteroneocystostomy through a stab wound in the bladder.

of operation but becomes evident in the subsequent days, the surgeon can and should try to pass ureteral catheters to the kidneys to splint the defective portion if possible. Re-exploration to remove a ligature is tempting but has had most unfruitful results. Nephrostomy is faster and safer; even ureterostomy in situ is better than to attempt to re-explore the ureteral area in the postoperative period. Subsequently, the obstructing catgut may dissolve and the ureter spontaneously reopen. If it does not reopen, at least the patient is in better condition than she would be otherwise for future re-exploration at minimal risk.

Summary

Although ureteral injuries occur in less than one per cent of the pelvic operations for benign lesions, they are accepted as a hazard in any gynecologic procedure. The reason for such injuries is primarily related to the proximity of the ureter to the uterine artery and to the infundibular pelvic ligament.

In an abdominal pelvic operation complicated by extensive endometriosis or pelvic inflammatory disease with the attendant difficulties in mobilization of tissues and the possibility of bleeding, ureteral damage is more likely to result.

To prevent this damage, the surgeon should identify and expose the ureter and check its position throughout the procedure.

In the management of a crushed or ligated ureter, a ureteral splint and soft rubber drains are useful. If the defect is low, ureteroneocytostomy may be necessary; if the defect is large, tissue, preferably from the ileum, can be used for a conduit. The ureter can regenerate rather large defects but cannot withstand stretching and tension. An enlarged infected ureter does not necessarily indicate nephrectomy. Prophylaxis is still the cardinal principle in management.

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Identity

Identity is man's most personal and prized possession. In part, we create it for ourselves; in part, society gives it to us. Secure in our identity, we flower; without identity we founder. — National Observer

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You will never get me to support a measure which I believe to be wrong, even although by doing so I may accomplish that which I believe to be right.

— Abraham Lincoln

Most folks have presence of mind. The trouble is absence of thought.

— Howard Newton

Polycystic Disease of the Liver with Hepatomegaly*

SINGLE CONGENITAL cysts of the liver are not uncommon findings at laparotomy or at routine autopsy. Multiple simple cysts of the liver, frequently occurring in association with polycystic kidneys, are less common. Polycystic disease of the liver which causes gross hepatomegaly is rare.

Several interesting case reports have appeared in the medical literature, some as indicated in the bibliography.[1,2,3,4] In reviewing these it becomes apparent that the condition is relatively benign and that the symptoms vary greatly with the degree of involvement of other organs and the size attained by the polycystic liver.

Case Report

A 51-year-old white housewife was admitted to St. Luke's Hospital in November 1957. She complained that her abdomen had enlarged gradually during the preceding year and an irregular lump was appearing near the umbilicus, which she surmised was probably a hernia. Associated complaints were belching and flatulence, a sensation of rapid filling when eating, urinary stress incontinence, weakness and fatiguability. Her past health had been excellent without significant illness, injury, or surgery. She had borne six children (all pregnancies normal), the last in 1949. Prior to this 1957 admission she had not seen a physician since her last postpartum examination eight years previously. A review of her parturition records gave no hint of liver dysfunction or enlargement. The family history was not significant. Four of six siblings were living and well, two having died of accidental injuries.

Physical Findings

Physical examination at admission was essentially negative other than the gross enlargement of the abdomen and hypochromic anemia (Fig. 1). Palpation of the abdomen revealed large, irregular, nontender tumor masses extending from the costal arch to the suprapubic area. These masses could also be palpated per vagina and together with a moderate cystocele explained the stress incontinence. Gastrointestinal X-ray examination was reported as negative except for some displacemement of the stomach and the appearance of a smooth but constant defect in the left upper cardia. Laboratory studies revealed a hypochromic anemia with hemoglobin value 8.2 grams (57%), red blood count 4,090,000, and white blood count 6,400; differential counts and morphology study of the peripheral blood cells were normal other than the hypochromicity. Urinalysis was normal; stool-guaiac negative; blood Kline negative; serum bilirubin low normal (direct and indirect); cephalin floculation test negative, and the bromsulphalein excretion time normal.

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*Presented to Minnesota Surgical Society at Duluth, Minnesota on July 12, 1963.

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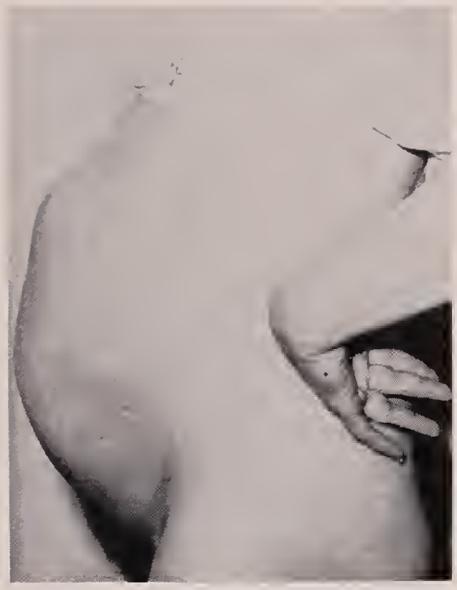

Fig. 1 — *Polycystic liver with hepatomegaly:* Showing contour of abdomen.

Operative Findings

Because of unusual clinical features the abdomen was explored 11/26/57 through a short left upper paramedian incision (Fig. 2). Upon opening the abdomen a huge liver, completely obscured by innumerable cysts, ranging in diameter from a few millimeters to 10 to 15 centimeters, filled the anterior, abdominal cavity and extended from the diaphragm down to the pelvis. Except for a small area (four or five centimeters in diameter) on the superior-anterior surface of the right lobe, there was no recognizable liver surface. A small wedge biopsy was taken at this point. Satisfactory exploration of the pylorus, gall bladder, and pancreas was impractical because of the overlying cystic masses. The kidneys and spleen were readily palpated and appeared to be normal in size and free of cysts. By passing the hand over the superior surface of the liver, cysts were found occupying the entire subdiaphragmatic space, and large cysts lateral to the gastric cardia obviously explained the extrinsic pressure deformity of the stomach as reported by the radiologist. The pelvic organs were normal and the ovaries grossly free of cystic disease. No free fluid or transudate was present in the abdomen and all peritoneal surfaces appeared to be free of adhesions or inflammatory changes. Several larger cysts were aspirated of clear watery fluid. Microscopic sections of the biopsy showed normal liver architecture with occasional small cysts (Fig. 3) lined with regular cuboidal epithelium.

Postoperative Course

There was no significant postoperative morbidity. At discharge the patient was instructed to limit moderately her sodium intake, and 50 mg. Hydrochlorthiazide daily was prescribed. During the subsequent six years her condition did not change significantly and it appeared that no progression or increase in the size of the cystic liver had occurred. She has continued in good health and has been able to pursue her usual activities with reasonable comfort. She mentioned, however, that discontinuance of the diuretic medication for a period of two or three weeks brought about increased discomfort and enlargement of the abdomen.

She was rehospitalized for evaluation in March 1963. Again her general physical condition was satisfactory except for the comparable enlargement of abdomen and recurrence of anemia (hemoglobin 10.4 grams). Urinalysis was normal, as was her blood pressure at 140/90. Other laboratory data were: total serum bilirubin 0.2, bromsulphalein excretion time normal, alkaline phosphatase 6.7 units, BUN 13 milligrams %, serum sodium 142 m/eq, serum potassium 4:0m/eq, and cephalin flocculation test ± at 24 and 48 hours.

With a view of acertaining possible changes in the portal circulation, blood volume studies were carried out by Martin,[4,5] using the Coomassie Blue Dye method recently described by him. The plasma volume was 3.182 l. (47 ml. per kg.) and red blood cell volume 1.557 l. (23 ml. per kg.). The rapid disappearance of the dye from the circulation over a two-hour period was additional evidence of normal liver function.

Following this study the patient's medication was changed to Aldactazide (2 mg. daily) as replacement of the Hydrochlorothiazide alone. Control of the symptoms appeared to be equally as satisfactory during the ensuing six months with this medication, and the patient continues her activities without unusual discomfort or complaint.

Discussion

No previous case of gross hepatomegaly due to polycystic disease appears in the records of the pathology laboratories of the Duluth hospitals during the past forty years. A casual search by Hebbel[7] of the pathology records at the University of Minnesota yielded two cases. In one of these the liver weighed 8,550 grams; in the other it was enlarged by a huge cyst containing six liters of fluid and by multiple other cysts of varying sizes, some as large as 18 cm. in diameter. Watson[8] recalled two cases of huge polycystic liver disease in identical twins. Feldman,[8] reviewing collected autopsy series, reports a 0.53% incidence of polycystic liver disease of all degrees of involvement. Bell[10] reported a study of fifteen cases of polycystic disease in which the weights of the livers were in excess of 2,000 grams, the largest weighing 9,510 grams. Henson et al.[11] collected twenty-nine cases of polycystic liver disease in the Mayo Clinic. Of these, twenty-three were palpable and only six extended to the umbilicus or below.

Polycystic disease of the liver has been described by authors[12,13,14,15,16] of leading pathology textbooks as a congenital malformation of the bile ductules which fail to connect with the biliary tree, resulting in the formation of retention cysts. Their presence is frequently associated with cystic changes in other organs, as the pancreas, ovaries, and most commonly the kidneys (this association variously reported as occurring in 50% or more of cases of polycystic liver disease). The cysts are described as lined with cuboidal or columnar epithelium and usually filled with clear fluid. Although a neoplastic etiology has not been implied by others, Popper[16] considers multiple microhamartomas arising in bile ductules a lesion related to polycystic disease of the liver.

The benign course of the disease is stressed by all authors. Congenital in nature, the rare case which progresses to hepatomegaly usually remains asymptomatic until the fourth or fifth decade. Bell[12] describes evidence of pressure atrophy of adjacent liver tisue by the multiple enlarging cysts in such unusual cases. Popper[16] describes a circumstance wherein large cysts in the inferior aspect of the right lobe have caused biliary obstruction requiring surgical intervention. Henson, Gray and Dockerty[11] have discussed surgical implications which may be involved in the management of polycystic liver disease. Clagget and Hawkins[17] have also discussed surgical treatment of polycystic liver disease

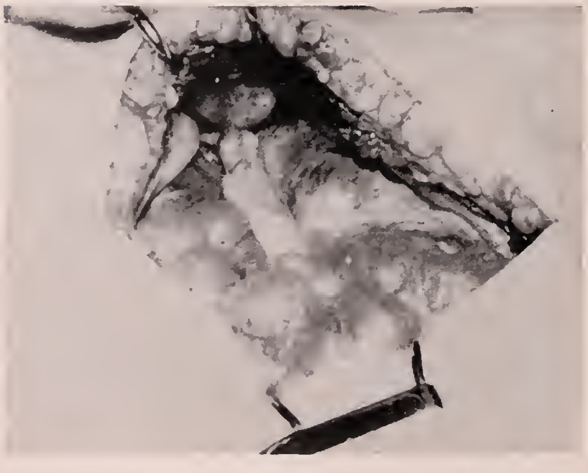

Fig. 2 — *Polycystic liver with hepatomegaly:* Showing mass of cysts thru left upper paramedian laparotomy incision.

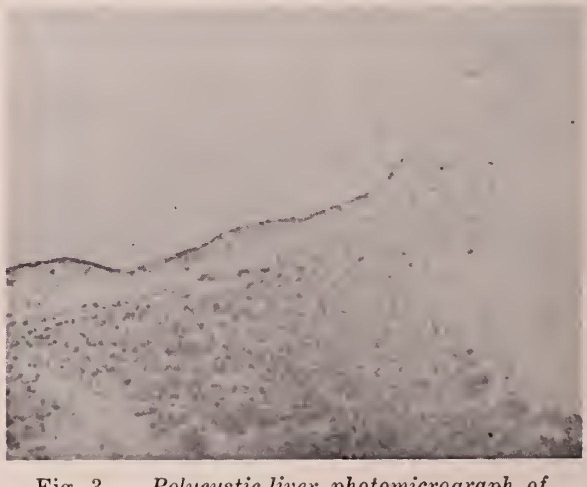

Fig. 3 — *Polycystic-liver photomicrograph of biopsy taken at laparotomy:* Showing normal liver architecture between cysts lined with regular cuboidal epithelium.

and report a case in which the disease was confined almost entirely to the left lobe which was successfully resected.

Summary

A case of polycystic disease of the liver with unusual hepatomegaly has been treated and observed over a period of six years. The implication is offered that sodium restriction and diuretic therapy may be of value in controlling the symptoms and the progress of the disease.

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Antimonks

"There was in the seventeenth century considerable controversy as to whether antimony was a remedy for disease or only a poison. The general opinion favored the latter view and the use of antimony in medicine had nearly ceased. The derivation of its name suggested its poisonous nature, for, according to legend, it came about in this way. An alchemist mixed some of the metal with grain and fed the mixture to hogs. They became fat. He drew an illogical conclusion from the two events — eating the antimony and getting fat. He attributed the fat to the antimony. Next he sought to apply his conclusion. Some monks of his acquaintance, in a monastery, had become thin and emaciated from their prolonged religious fasts . . . He fed them antimony to make them fat. But instead of getting fat they died. In consequence he decided that the metal was not good for monks, and so he named it antimonks, or in the French, antimony."*

---

*Haggard, Howard W., M.D.: "The Lame, the Halt, and the Blind," p. 36.

Argument develops more heat than light — discussion the converse —

Enzymic Steroid Conversion in a Granulosa Cell Tumor

M. J. BRYSON, Ph.D.*
I. H. KAISER, M.D., Ph.D.*
M. L. SWEAT, Ph.D.*
Salt Lake City, Utah

THE RAPID progress in recent years in the development of techniques for the detection of individual steroids has made possible the detailed study of the production of these substances by tissues in vitro. This has in turn permitted the examination of differences between normal endocrine tissues and endocrinologically active tumors, a matter of much interest in view of the light which the behavior of neoplastic cells may shed on normal physiology.

The steroid metabolism *in vitro* of one granulosa cell tumor has been reported. The present paper is concerned with enzymic steroid conversions in a second such ovarian tumor.

*Abstract***

A nine-year-old girl was seen with a chief complaint of early menstruation. She had developed pubic hair, vaginal bleeding of irregular pattern and some breast development. She was also advanced in growth. On examination an 8-cm. mass was found in the pelvis. At exploratory operation and upon histological examination this was found to be a solid tumor replacing the right ovary and having the characteristics of a granulosa cell tumor.

The metabolism of steroid hormones in vitro by this tumor tissue was studied, using progesterone-4-C^{14}, 17αOH-progesterone-4-C^{14}, testosterone-4-C^{14} and androstenedione-4-C^{14} as substrates. This study demonstrated a high capacity for estrogen synthesis from all of these substrates, in contrast with the findings in normal ovary. In addition the tumor formed 11-deoxycorticosterone. The remarkably increased production of estrogen by this tumor is certainly capable of producing the clinical syndrome observed in the patient.

***Editors' Note: This manuscript was published in Minnesota Medicine 46:1235, 1963. The title was inadvertently incomplete. Because of the significance of this manuscript the title page is hereby reprinted and an abstract attached.*

---

*Department of Obstetrics and Gynecology, University of Utah College of Medicine, Salt Lake City, Utah.

Anybody can win, unless there happens to be a second entry. — George Ade

Stenosing Tenosynovitis of the Thumb in Children

KENATH H. SPONSEL, M.D.
Minneapolis, Minnesota

SPONTANEOUS FUNCTIONAL loss of the thumb in infants and children is generally due to a narrowed tendon sheath at the level of the head of the first metacarpal or to a fusiform enlargement of the flexor pollicis longus tendon. Both of these conditions can exist simultaneously.

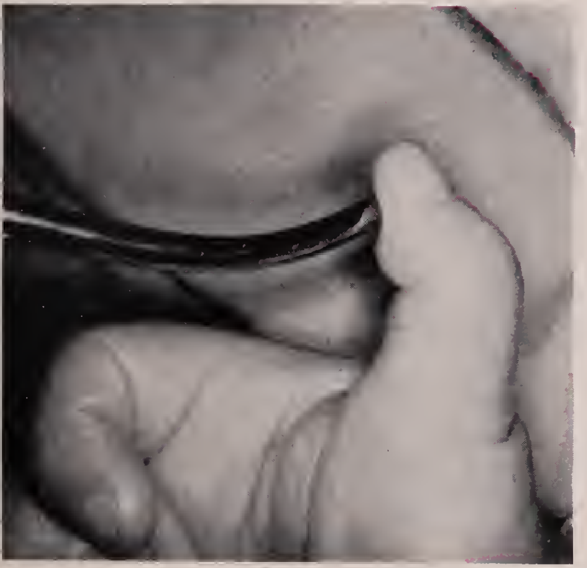

Fig. 1 — Under anesthesia, the thumb could not be pushed into extension.

Clinical Manifestation

The mother usually reports that the distal phalanx of the thumb snaps from extension into flexion or vice versa. As the condition is allowed to remain, the thumb may finally be locked in flexion (Fig. 1). Under such circumstances the child does not use the hand normally because of loss of facility. This condition has been called "trigger thumb,"[1] or "dislocating thumb."

The physical examination reveals that the distal phalanx of the thumb is usually in flexion. The child will be found to avoid active motion and resist passive extension because of discomfort. In infants the thumb may be clenched into the fingers. As the phalanx is forced into extension, a snapping sensation is observed along the thumb and an enlargement of the tissue at the flexor surface of the metacarpophalangeal joint may be evident. Because of discomfort the patient will often pull the phalanx into flexion as soon as it is released from examination, though this maneuver is painful.

In some spontaneous resolution may occur, but it is possible for this condition to redevelop in adult life.

Etiology

In the infant or child no initiating factor has been observed, and it is thought that this may be developmental or congenital.

The findings at operation reveal a disparity in the gliding mechanism of the flexor pollicis longus tendon. The flexor sheath is narrow between the tendon of the deep head and the tendon of the superficial head of the short flexor muscles. This is the level of the sesamoid bones of the short flexor tendons in adult life. Most commonly the flexor pollicis longus tendon presents a fusiform enlargement over a distance of one-fourth inch. It is this enlargement which causes the snap as it glides distally to the tight sheath in extension and proximally to the sheath in flexion.

Treatment

The treatment of this condition is surgical. An incision is made on the radial side of the thumb midway between the flexor and the extensor surfaces (Fig. 2). The muscle body of the short flexors is a guide to the plane of the tendon sheath. The radial nerve of the thumb is retracted volarward in order to avoid trauma. Cautious incision on the volar surface of the tendon sheath for approximately three eighths of an inch at the level of the metacarpophalangeal joint releases the disparity in the gliding mechanism and provides the cure. After this is done, direct observation reveals the tendon enlargement riding freely in the region of the former constricting sheath. Only on rare occasions is it necessary to remove a wedge of tendon in order to reduce its size. Only the skin is closed with sutures and a bandage is applied.

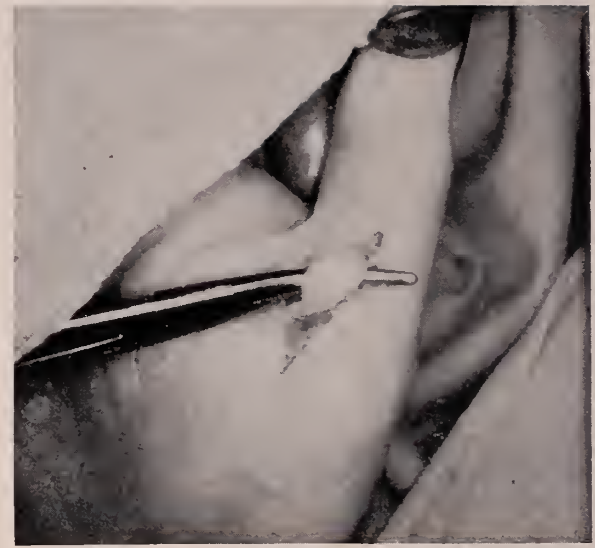

Fig. 2 — Note the incision, thickened tendon, and ability to extend.

Conclusions

In ten surgical cases, one of which was bilateral, incision of the sheath has restored normal function. No complications or recurrences have been observed.

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Let me have men about me that are fat,
Sleek headed men, and such as sleep nights
Yond Cassius has a lean and hungry look.
He thinks too much, such men are dangerous.
Julius Caesar — Shakespeare

The Internal Revenue Service is a far-flung operation, an octopus with 20 percentacles. — Changing Times

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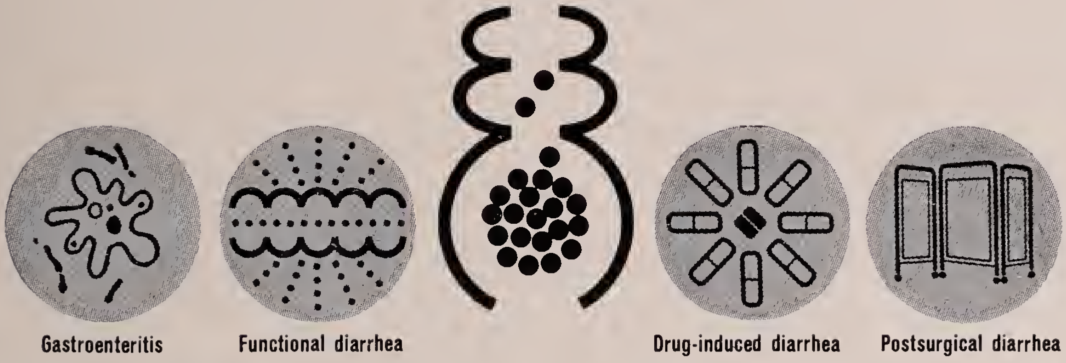

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*Donnelly, J.: A.M.A. Arch. Environmental Health 6:697, June, 1963

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Editorials

Bilateral Mastectomy for Unilateral Carcinoma of the Breast

Some small series of figures have shown that carcinoma of the breast is found bilaterally in from 1 to 4 percent of patients who suffer from that disease. Other figures indicate that, when all organs of the body are considered, multiple carcinoma occurs in from 1 to 3 percent of patients suffering from cancer.

If then, one adopts the policy of recommending prophylactic simple mastectomy for the opposite breast, as has been done by Sanders and others, one might also recommend excision of some other organs which occasionally harbor carcinoma.

Figures have shown that on first operation a fairly sizable percentage of breast cancers have mediastinal or supraclavicular lymph node metastases. These areas are relatively inaccessible to all except the very courageous surgeon; therefore, until a more satisfactory method has been devised for eradicating with certainty the primarily involved breast and its initial metastases, it would seem redundant to recommend the routine removal of the uninvolved contralateral normal breast. Such a procedure would carry caution to the point of radicalism.

The incidence of fibrocystic disease of the breast has been reported to be as high as 53 percent in one series of autopsies and is generally considered to be clinically evident in at least 13 percent of women.

The incidence of carcinoma in 385 patients with benign tumors of the breast was found to be 1.8 percent. In chronic cystic mastitis this incidence was 2.6 percent, and it has been indicated that fibrocystic disease is always bilateral.

If, then, we reason that the contralateral breast should be removed when one breast is involved with carcinoma, we might also reason that bilateral adenomammectomy should be done for chronic cystic mastitis in order to diminish the possibility of carcinoma by eliminating most of the carcinoma-bearing portion of both breasts.

Though radical mastectomy has not proved to be adequate for carcinoma of the breast when the lymph nodes of the mediastinum are involved, contralateral, simple mastectomy in addition to radical mastectomy in the involved side would seem to be more surgery than required.

Carl O. Rice, M.D.

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CSO-1054

The Fallacy of Deceptive Techniques in the Patient with Incurable Malignancy

INCURABLE MALIGNANCY presents many unsolved equations, yet the search for answers to the questions of etiology, early diagnosis, and tumor-specific treatment is being carried forward relentlessly. Basic to this problem lies the physician-patient relationship. Taken as a whole, this human equation is also sprinkled liberally with unknown quantities; but there is one question which would appear soluble: should the individual with incurable malignancy be told the truth?

The perennial discussion of this question in both professional and lay publications attests to the diversity of views and also to the errors of perception on the part of many physicians and laymen. Gilbertsen and Wangensteen[1] point out the advantages of informing nearly all patients of their diagnosis. Their report also indicates that cancer patients themselves are overwhelmingly in favor of being told. In the same publication,[2] Bowden asserts that cancer patients should be informed only when special circumstances make it important that the individual become aware of his prognosis. He suggests that obliquity and dissuasion be used to guide the patient.

The objective of this paper is the exploration of the fallacy involved in the willful attempt to deceive the patient with incurable cancer. One illustrative case will be used to demonstrate this fallacy.[3]

On 3 June, 1963, in Italy an 81-year-old man died of a gastric malignancy. Gastric hemorrhages were first noted in November, 1962. The lesion was judged nonresectable and bleeding was associated terminally with azotemia. Because he was a respected and honored world figure, his personal physician was interviewed shortly after the demise. Several quotations from this interview are of interest: "The weapon of hope is used for every patient;" "We tried to deceive him as long as we could;" "We told him it was a gastric inflammation."

Then the patient is reported to have answered: "I have my suitcase packed."

This cogent answer indicates that the attempt to deceive the patient, and the effort to conceal the truth, were as vain in this case—as in many another.

Patients with incurable cancer may be divided into several groups according to their desire to be truthfully informed of the type, extent, and implications of their disease:

A. Those Who Want to Know

This patient accepts the possibility of cancer prior to diagnostic procedures, and usually requires the physician to give him all the facts when the facts are known. He expects to be told both diagnosis and prognosis. He joins the physician and participates actively in the diagnosis and treatment of his disease. The attitude of such a patient precludes the use of falsification.

B. Those Reluctant to Know

This patient exhibits the "normal" fears and apprehensions about cancer, asks for the diagnosis and prognosis, but is guarded in his response and acceptance of the facts. He usually requires repeated and simplified explanations of his situation, possible treatments, and future life. He may exhibit transitory depression and rejection of facts, but will usually acquire a level of normal adjustment to the inevitable.

The perceptive physician can use only the truth in his attempt to promote equanimity and understanding.

C. Those Who Accept in Silence

This patient "knows" of his cancer before his first examination, or he becomes aware of the gravity of his disease at some point during the intensive diagnostic precedures. Something in the nature of his illness, his physician's reputation, or the diagnostic examinations give him indirectly the information that was so actively pursued by patient A. Patient C may never ask any direct questions of his physician but may guardedly discuss his situation on his own terms. Occasionally the physician will be puzzled by this attitude and will wonder whether Mr. Jones is actually in possession

(Continued)

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of sufficient facts to plan his future. If this is a point of doubt, a simple question, such as: "Do you know what's wrong with you?" or "What are your plans?" will produce a knowledgeable answer or provoke further questions and answers which will place both physician and patient on a level of basic understanding.

D. Those Who Reject the Diagnosis of Cancer

Unwilling or unable to face the prospect of death from cancer, a patient of this type will often delay medical advice until some complication of his malignancy forces him to accept emergent care. The events attendant on his hospitalization are usually of sufficient gravity to breach the wall which was constructed by the patient's fear. A more co-operative patient in this group will accept recommendations and treatments but stolidly refuse to discuss his malignancy. This refusal to verbalize is mute evidence to the physician that he is fully aware of his situation but unwilling to talk. Occasionally a patient in this group will reject the diagnosis completely and begin a round of consultations at the next larger medical center; or he may even consult a quack—vainly pursuing the false promises of nonscientific cures and nostrums.

Conclusion

Thoughtful consideration of these groups leads to the conclusion that, in one way or another, the patient with cancer learns the truth about the nature of his disease. Whom then are we deceiving when we willfully withhold the information sought? When the physician deliberately attempts to conceal the truth, he is deluding and deceiving only himself. When the patient presents himself for examination he is in fact asking for an answer to the question: "What is wrong with me?". Every patient must be gently and tactfully observed and his reactions judged and weighed on an individual basis.

After examination, X-ray studies, and exploration or biopsy, the responsible physician must answer all questions asked. Details of tumor extent, prognosis, and predictable disability may be left to the circumstances of the situation; but adequate and honest answers are incumbent upon the physician. Such forthrightness requires both courage and experience and a willingness to devote additional time at the bedside of the patient. The difficulties are many, but the rewards include better understanding and a patient willing to accept new procedures, new treatments aimed at longer palliation, and the "hoped-for" day of cure.

John V. Thomas, M.D.
Duluth, Minn.

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Few in public affairs act from a mere view of the good of their country whatever they pretend—fewer still in public affairs act with a view to the good of mankind.
— Benjamin Franklin

The Lord hath created medicines out of the earth; and he that is wise will not abhor them.—Aprocrypha: Ecclesiasticus

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Polycystic Liver

Congenital polycystic disease of the liver is rare but interesting. Many physicians will not see this condition during their lifetime. The case reported in this issue by Dr. Eckman is a classical example. The patient, usually a female, presents with an enlarged liver and right abdominal distress, appears not particularly ill, and all the liver function tests are paradoxically "normal." The liver often feels "nodular" and at first metastatic carcinoma is suspected. More careful palpation may reveal that the "nodules" are fluctuant like a cyst. The patient may also give a history of known hepatomegaly for more than a year without systemic deterioration, thus arguing against a progressive malignancy. With these findings and a normal value for blood urea an excretory urogram should be obtained to determine whether polycystic kidneys are present. The observation of increased urea with a cystic liver suggests associated renal complication. In Comfort and co-workers'[1] series of 24 patients with polycystic disease of the liver, 50 per cent also had polycystic kidneys. One or both kidneys may be palpable in addition to the hepatomegaly. The right diaphragm may show contour changes from hepatic cysts on a routine roentgenogram of the chest. The cholecystogram may show the gallbladder shadow indented by multiple small cysts or show the organ in an unusual position; generally it will be normally functioning.

The finding of marked hepatomegaly with "normal" sulfobromophthalein retention should always "ring a bell," causing the clinician to consider polycystic hepatic disease, cavernous hemangioma of the liver, and hemochromatosis. A cavernous hemangioma will usually not feel nodular and, rarely, an area may be compressible like a sea sponge, whereas in hemochromatosis the surface of the liver is firm and smooth unless associated with hepatoma. Rarely normal excretion of sulfobromophthalein is seen with the hepatomegaly of cirrhosis, metastatic carcinoma or amyloid disease, but other clinical data are usually present.

Because of the extensive practice of needle biopsy for diagnosis, the use of this procedure in polycystic disease requires special comment. It is difficult to obtain a satisfactory specimen, especially of cyst-wall tissue, with a needle in polycystic disease to confirm the diagnosis pathologically. Severe reactions with abdominal pain may occur after rupture of a cyst with a Silverman needle. When this disease is suspected, the cystic cavity can be aspirated directly with a 21-gauge needle in one or multiple areas, with removal of varying amounts of clear or bile-tinged fluid. This observation essentially establishes a diagnosis. Although surgical exploration has been done in most reported cases, it is not necessary if the disease is clinically suspected and the aspiration technic performed. In two unreported cases associated with jaundice and fever, large cysts were anastomosed to the jejunum. Surgical procedures are rarely of value.

As in Dr. Eckman's case, patients with this disease may live many years with minimal disability. Eckman's suggested treatment by diuretics and sodium restriction certainly merits a trial to diminish the abdominal pressure and discomfort.

Maurice H. Stauffer, M.D.
Rochester, Minn.

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Tyrant

Writing a book was an adventure. To begin with it was a toy, an amusement; then it became a mistress, and then a master, and then a tyrant.—Winston Churchill

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Letter to the Editor:

Dear Doctors Rice, Berman, et al:

The March issue of Minnesota Medicine published a footnote after my name: "Posthumous." Many years ago Mark Twain, in commenting on a similar premature statement, declared it to be an exaggeration. I now do the same. Please give my disclaimer the same publicity the notice got, although it will never catch up with the original report. How great the exaggeration, time alone will tell. It is true that my ninety years have accumulated many disabilities and accompaniments of the aging process. The racer has been slowed, but the poor wight, somewhere down the line of authority, like so many of us, thought a dream was a reality and tried to score a scoop. Please caution him, but gently, next time to check with the authorities. I hope the God-given spiritual body has not been so badly mauled as has the natural body.

With kindest regards to you all, I am,

Sincerely yours,
S. Marx White, M.D.

Dear Dr. White:

I suppose the last word on the premature obituary was written by Mark Twain about 75 years ago when he stated that the news of his death was somewhat exaggerated. I suppose also that an editor can commit no worse error than to kill off one of his valuable contributors before his time.

I know that there is no proper apology that one can offer for mistakes such as this. All I can tell you is that it was unintentional. You know, of course, that no one in this state or in the world wishes you anything but good. Thanks for your indulgence. With all good wishes for the future, I am

Sincerely yours,
Reuben Berman, M.D.

Dear Dr. White:

In humble apology I hereby publish my own obituary in the hope that I may gain the distinction of surviving with the honor and fame which you and other great men have attained whose obituary preceded their demise:*

"Did you hear the editor of Minnesota Medicine died last night — how about a game of golf," etc, etc.

Sincerely,
Carl O. Rice, M.D.

---

*Hemingway, 1954.

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Curbstone Consultation

Osteomyelitis

QUESTION: A 13-year-old girl sustained a relatively minor fracture of the posterior of the tibia and a short leg cast was applied. Three weeks later the leg was considerably swollen and six weeks later an obvious osteomyelitis was evident. Antibiotics were then given and the systemic symptoms subsided, but a sinus tract developed in the leg. Could this have been prevented? *M.D., St. Paul*

ANSWER: Timing of antibiotic therapy is most important in the control of this condition. The antibiotic therapy may be effective in overcoming the systemic manifestations, but ineffective in overcoming the local lesion. Insofar as the lesion is concerned, the antibiotics must be administered in plentiful amounts before the lesion walls off. Otherwise, the antibiotics become ineffective. In this case, even with antibiotic therapy, the systemic manifestations subsided while the local symptoms increased. Early decompression of the involved area could probably have prevented the ischemic necrosis. There is still some disagreement as to the best time for surgical intervention. The timing is often quite difficult. After a few days, if the local symptoms do not subside, then the area should be opened. A simple incision through the skin and several large drill holes or a window through the bone, is usually all that is necessary. The area is flushed with antibiotic solution, the window is closed, and antibiotic therapy is continued.

J. Gordon McAllister, M.D.
Ft. Lauderdale, Florida

Vitamin B_{12}

QUESTION: Is Vitamin B_{12} of value in the treatment of diabetic retinopathy? *M.D., Waseca*

ANSWER: There is no substantial evidence of Vitamin B_{12} deficiency in diabetics or that such a deficiency plays a role in the etiology of diabetic retinopathy. Therefore, therapy with Vitamin B_{12} would not seem to be indicated in the treatment of that condition.

Beware lest you lose the substance by grasping at the shadow.—Aesop

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I am a member of the rabble in good standing.— Westbrook Pegler

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Fracture — Trauma Conference

Intertrochanteric Fracture —

Treatment by Traction

Intertrochanteric fractures of the femur are, for the most part, straightforward surgical problems, where, at the earliest convenient time, reduction should be accomplished and then maintained with a fixed angle nail and plate. Subsequent to fixation the patient can usually be mobilized, thus obviating the significant morbidity and mortality that accompany prolonged bed rest in the older patient.

The advantages of such a vigorous approach over the old conservative prolonged traction technique have been statistically demonstrated in large comparison series.[1-2] Nevertheless, when the fracture is so comminuted that the chance of achieving a good stable fixation at surgery is poor, it would seem preferable to not operate but rather to rely on skeletal traction for the reduction and immobilization of the fragments.

The following cases are of interest.

Case History

Case 1:

A 66-year-old female was admitted to Minneapolis General Hospital on July 26, 1960, after being struck by an automobile as she crossed the street. She had an obvious right hip fracture and appeared somewhat confused. X rays of the hip taken in the emergency room revealed a comminuted intertrochanteric fracture. X rays taken of her skull revealed no fracture (Fig. 1).

She was transferred to the fracture ward and there it was noted that a significant hematoma was developing about the right hip and her blood pressure began to fall. A blood transfusion was started and it was elected to reduce and immobilize the fracture, utilizing skeletal traction through the tibial tubercle. This was accomplished. Consideration was given to opening the fracture site immediately in an attempt to control the bleeding, but it was felt that the major vessels were intact and the surrounding tissue would soon tamponade the bleeding points. However, it required 4,500 cc. of blood over a 24-hour period to replace the sequestered blood. The swelling reached a maximum during this time, there was no further significant change in the size of the patient's thigh, and her hemoglobin stabilized at 12 gm.%.

As the hours passed during that first day she became less responsive and neurosurgical consultation was obtained. In consultant's opinion the presence of petechiae over the neck, chest, and shoulders indicated that a fat embolism had occurred. She was treated with intravenous 10% alcohol without immediate effect. However, during the next several days with only supportive care her sensorium began to clear and by the end of a week she was near normal. The hematoma of her right thigh and hip gradually subsided. On October 4, 1960, she was taken out of traction and placed in a single body spica and finally discharged to a nursing home on the 14th of October.

Continued

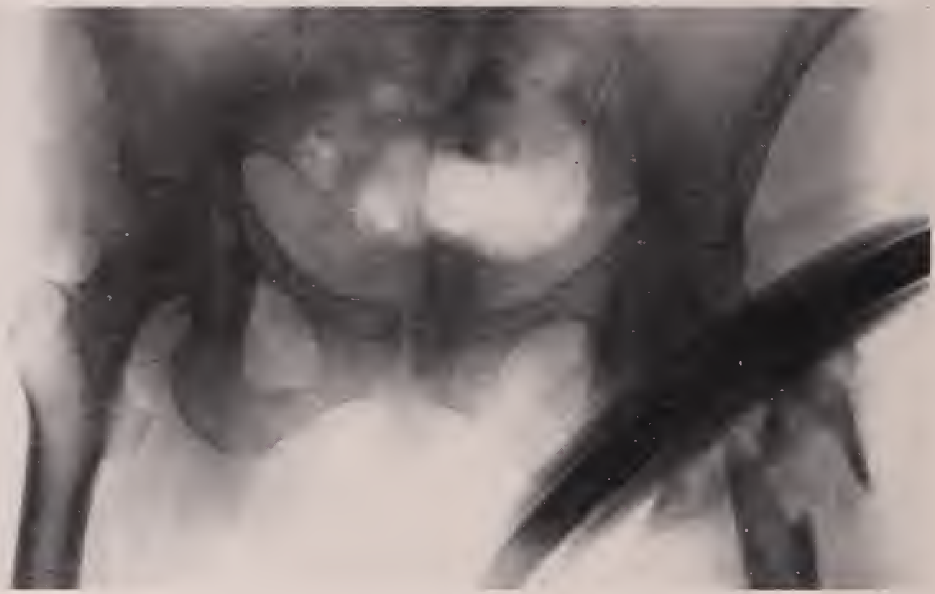

Fig. 1 — Comminuted intertrochanteric fracture of pedestrian.

Case 2:

A 28-year-old man was working as a tree trimmer when he slipped from his perch and fell approximately 20 feet to the ground, landing on his right hip. He was brought to Minneapolis General Hospital and X rays were taken, revealing a comminuted intertrochanteric and subtrochanteric fracture of the right hip. Admission date, February 3, 1962 (Fig. 2).

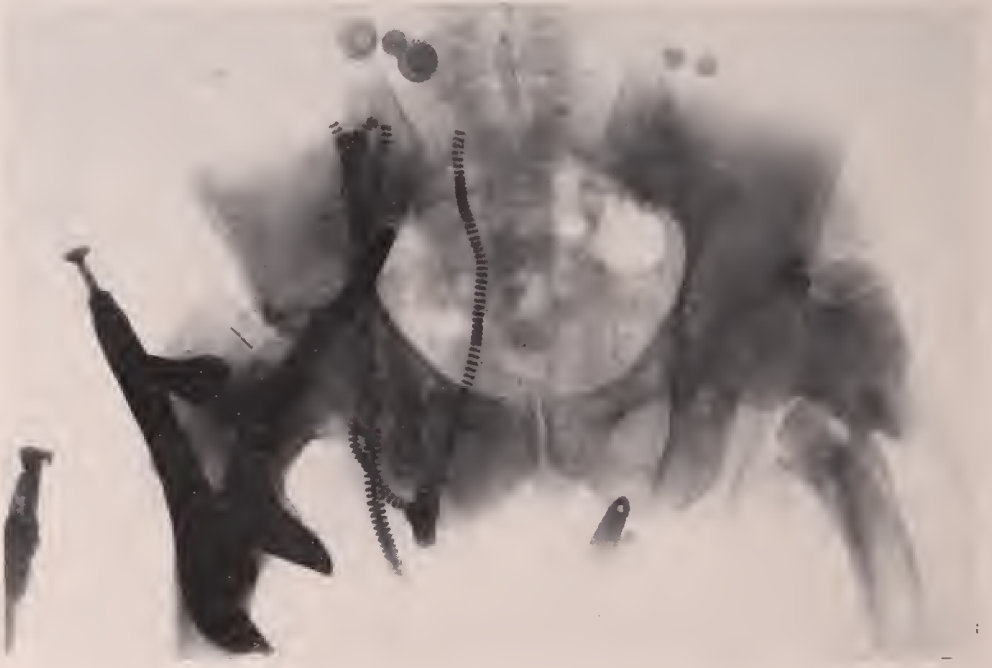

Fig. 2 — Comminuted intertrochanteric and subtrochanteric fracture of tree trimmer.

After transfer to the fracture ward his blood pressure began to fall and it was noted that there was an increase in the swelling about the right hip. A blood transfusion was started. One-thousand cc. of blood were given during the first 24 hours.

Careful study of the X rays revealed such comminution at the fracture site that it seemed rather unlikely to the *Fracture Conference* that sound fixation could be achieved at surgery. Therefore, he was placed in skeletal traction with a Kirschner wire through the tibial tubercle.

The patient did very well in traction and on April 19, 1962, ten weeks following his fracture, his traction was removed and a single body spica was applied. He was discharged to the care of his private physician on April 24, 1962.

Discussion

That all intertrochanteric fractures cannot be considered routine is amply demonstrated by Case 1. Without the benefit of early blood replacement the patient may well have succumbed to a soft tissue hemorrhage. Supportive care during the period of coma secondary to her fat embolism was also a necessary part of her treatment. This case is a reminder to all physicians caring for patients with such injuries that dire complications may arise prior to the definitive reduction and immobilization of their fractures but that a successful outcome may result if close observation of the patient reveals these complications early and prompt treatment is initiated. If traction is elected as the means best suited to immobilize the patient's comminuted fracture the physician must be alert to the development of, and better still, prevention of, such complications as pneumonia, decubitus ulcer, urinary tract infection, and pulmonary embolism.

Harrison H. Farley, M.D.
Minneapolis, Minnesota

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1. Taylor, G. M., Neufeld, A. J., and Janzen, J.: Internal Fixation for Intertrochanteric Fractures. J Bone Joint Surg 26:707, 1944.
2. Cleveland, M., Besworth, D. M., and Thompson, F. R.: Intertrochanteric Fractures of the Femur — A Survey of Treatment in Traction and by Internal Fixation. J Bone Joint Surg 29:1049, 1947.

The Cost of Things*

Buying a new shirt or three pairs of nylons or having a prescription filled all cost about the same. The average prescription cost $3.26 at the end of 1962. At the same time the average earning of U. S. manufacturing production workers was $96.96 per week, and it took the worker an hour and 22 minutes to earn enough for his prescription cost. A carton of cigarettes was worth an hour's labor. The average employee worked nearly three hours for a tooth extraction, 44 minutes for a haircut, half an hour for a six-pack of beer and 25 minutes for a movie ticket. In the prescription category, a 51-minute "bargain" was a dozen tablets of lifesaving penicillin.

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Give us clear vision that we may know where to stand and what to stand for, because unless we stand for something, we shall fall for anything. — Peter Marshall

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Death horrifies us not so much by what is beyond it as by what we might have done and didn't do on this side of it. — Edward Coursin

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Earth's the right place for love: I don't know where it's likely to go better.
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Tumor Conference

Chronic Leg Ulcer

Mrs. P. H., 74, has been in excellent mental and physical health except for an ulcer on the lateral aspect of the left ankle. This has been present for three years and developed without incident or trauma. Approximately three years ago she was hospitalized in another city for this condition, and she states that on that occasion four biopsies were taken from the ulcer. These were reported as showing only ulcerated and chronically infected tissue. Several months of hospital treatment at that time resulted in no improvement and until now only dry dressings have been used. There has been no limitation of activity.

Physical Findings

One year ago the ulcer measured 6 by 8 cm. and it continues to remain that size. It is situated over the lateral malleolus of the left ankle and is surrounded by an area of induration in which there is a 2-cm. rim of erythematous tissue. There is no ankle or foot edema. The skin is dry and flaky over the entire lower extremity. There are no varicose veins or unusual areas of pigmentation. The dorsalis pedes and the posterior tibial artery pulsation was not evident. Femoral arteriogram was done on September 6, 1963, and showed excellent arterial circulation with normal runoff.

Culture from the ulcer showed coagulase, positive staphylococcus aureus. Treatment with elevation, moist packs, and antibiotics resulted in marked improvement in the appearance of the ulcer but there was no change in its size or character.

Biopsy Findings

Biopsy of the ulcer was performed on August 27, 1963. The biopsy specimen was pie-shaped and extended from the normal skin to the center of the ulcer and to the fascia. The pathologist's report indicated only chronic inflammatory tissue.

Treatment

On September 13, 1963, the entire ulcer and surrounding skin were removed down to the periosteum and a split thickness skin graft was

Continued

applied. The graft took well and the patient was discharged from the hospital.

The pathologist reporting on this specimen described a well differentiated squamous-cell carcinoma. During a routine postoperative visit one month later it was noted that there was recurrence of tumor in the lower half of the grafted area.

Etiology

It was at this time that additional history indicated that the patient recalled having received some X-ray treatment in 1942 for a chronic lichen planus and in 1952 for psoriasis. The physician who treated her was contacted and informed us that there was no record of the amount of X ray given.

Discussion

A squamous-cell carcinoma such as this could arise in chronically inflamed, scarred, or ulcerated tissue.[3-4] However, because of the absence of a history of trauma, this ulcer probably arose as a result of changes secondary to excessive radiation[1] received during treatment for chronic skin disease.

Low Voltage Radiation

It has recently been suggested that low voltage radiation such as is used in skin diseases is more prone to cause malignant degeneration.[2] The well known radiation dermatitis, burns, and later squamous-cell carcinoma which develop after excessive exposure to fluoroscopy and other diagnostic X-ray procedures implicates excessive exposure to all forms of X-ray radiation as a causative factor in squamous-cell carcinoma of the skin.

Recommended Treatment

Two approaches to treatment were suggested: (1) Wide resection of skin, muscle, bone, and fascia down to histologically uninvolved tissue with secondary graft or closure; (2) Below knee amputation.

It was the consensus of opinion that amputation was the treatment of choice, as wide excision would leave an extremity of doubtful usefulness and would require much longer hospitalization before healing occurred. Amputation, well done and properly placed, would result in a useful limb and would allow for certain wide excision of the tumor.

It was further suggested that an inguinal node dissection on the same side be performed approximately six weeks after amputation. This is to be done even in the absence of palpable lymph nodes in order to pick up any tumor cells which may have migrated through the lymphatics to this area. Catheter suction under the skin flaps to aid in primary healing of the skin flaps is recommended.

Since approximately 40% of the patients with lymph node dissections have some residual edema of the extremity, the fitting of the prosthesis should be delayed for six weeks following the second procedure.

Follow up:

Amputation was done; the specimen showed invasion of the fibula by tumor cells; inguinal node dissection showed no tumor in any node; no dependent edema developed and the patient has been fitted with a Prosthesis.

A. M. Sborov, M.D.
Minneapolis, Minn.

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1. Radiation as a Carcinogenic Agent, Radiation Review 3:272-280, 1955 Akerman & Regato III Edition, 1962
2. S.G.O.-117:5 559-562 Relationship between Radiation Injury to Skin and Malignant Change.
3. Sutton: XI Edition, 1956, 1213-1214 Trauma as a Cause of Cancer of the Skin.
4. Anderson: III Edition, 1957, 1165.

The Health of King James I

James I "came to the throne of England in the year 1603 . . . As a child he was unable to walk until he was six years old; his body was deformed, and all the rest of his life he walked with an awkward gait, usually leaning on the arm of one of his favorites. The cause of his deformity, as given at the time, was that he had been poisoned by the milk of a drunken wet-nurse. The truth of the matter is that James had rickets . . .

"If one may judge from pictures of his face and descriptions of his actions, he probably had enlarged tonsils and almost certainly an enlarged adenoid. There were no operations then to remove obstructions to breathing, and so his nose and upper jaw were deformed, and he held his mouth open. He had nasal catarrh, and since he had no handkerchief he did the best he could with the lace on the cuff of his coat. A most unkingly picture, but adenoids were natural then, and handkerchiefs were not.

"James' teeth decayed, and probably this was hastened by the deformity of his jaw. But there was no orthodontic treatment then to straighten out his teeth, nor dentistry to prevent decay or to repair its ravages. When his teeth had decayed down to the level of the gums he bolted his food. Quite naturally, he had indigestion. Having discovered that his colic became particularly severe whenever he was worried by matters of state, he thenceforth refused to allow matters of state to worry him.

"He had rheumatism — probably an after effect of his infected teeth — and his joints became so stiff that he had to be lifted onto his horse, from which he frequently fell. He developed gout and then malaria. There were then no curative treatments for malaria; for cinchona, or quinine, was not discovered until some time later. So King James died a natural death."*

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*Haggard, Howard W., M.D.: "The Lame, the Halt, and the Blind," p. 395.

Photographic Contest

The photographic contest continues. Send your color transparencies to the Photo Editor, Minnesota Medicine. See rules, page 34, January 1964 issue.

Anger is only one letter short of danger. — Indianapolis Transit News

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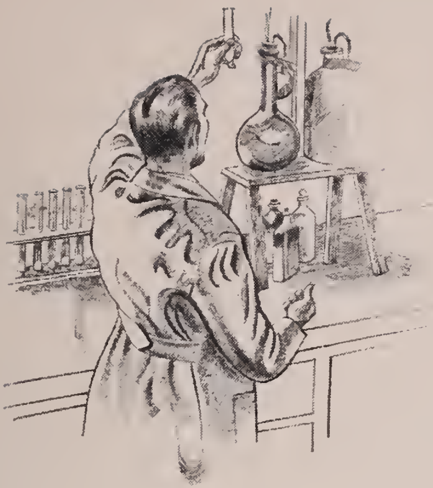

Clinical Path Conference

Nephrotic Syndrome and Thrombophlebitis

The patient, a dyspneic and edematous 57-year-old man, was admitted to the hospital for the fourth and final time on August 12, 1962.

Dyspnea and edema had been the chief complaints on the first admission one year earlier, in August 1961. He gave a history that following chilling, attacks of dysuria and costovertebral pain were also noted. The patient was susceptible to colds and was allergic to sulfa and tetracycline drugs.

Six years before the first admission, in 1955, there had been an episode of proteinuria and edema. Two episodes of illness in 1957 were recalled: one an attack of pneumonia associated with hemoptysis, the other thrombophlebitis of the lower extremities. Since then, edema of the lower extremities, more pronounced on the right, had continued.

The positive physical signs recorded during the first admission were: blood pressure, 200 mm. Hg. systolic and 120 diastolic; Grade I narrowing of the retinal vessels; Grade II apical systolic cardiac murmur; edema of the right leg.

Laboratory studies (Table 1) revealed anemia, mild azotemia, hypoproteinemia, hyperchloremia and proteinuria as the major abnormalities.

Diuretics and intravenous serum albumin were administered.

On the second admission, in January 1962, pedal edema and dyspnea had increased since the first admission and orthopnea had appeared. Except for certain elements the physical examination was essentially unchanged. The blood pressure in millimeters of mercury was recorded as 200 systolic, and 95 diastolic. The optic fundi revealed Grade III retinopathy with arteriovenous nicking and retinal scars and exudates. Slight tenderness was present in the right upper abdominal quadrant.

Laboratory studies (Table 1) revealed essentially the same abnormalities as on the first admission. In addition, elevated levels for creatinine and uric acid were observed. Treatment consisted in administration of blood and of diuretics.

During the third admission (May 1962) the patient was still dyspneic and hypertensive and exhibited Grade III edema of the lower extremities.

Continued

TABLE I
Admissions and Results of Laboratory Tests

Test	First Adm. Aug. 1961	Second Adm. Jan. 1962	Third Adm. May 1962	Fourth Adm. Aug. 1962
Hemoglobin (gm./100 ml.)	7.5	5.9→7.5	6.4	4.2→6.6
Hematocrit (%)		16.5	22	
Erythrocytes (per cu. mm.)		2,070,000	1,680,000	
Leukocytes (per cu. mm.)	5,750	4,850		
Erythrocyte Sedimentation Rate (mm. in 1 hour)	73			
Reticulocyte Count (per 100 erythrocytes)	2.3			
Blood Urea Nitrogen (mg./100 ml.)	61	64→56	69→134	126
Serum Creatinine (mg./100 ml.)		10.8→13.5	14.3	12.0
Serum Uric Acid (mg./100 ml.)		6.5		
Serum Calcium (mg./100 ml.)		7.3		
Blood Glucose (mg./100 ml.)	100	90		
Serum Albumin (gm./100 ml.)	2.9	2.5	2.3	2.2
Serum Globulin (gm./100 ml.)	2.1	2.5	2.2	2.2
Serum Cholesterol (mg./100 ml.)	235	245		
CO_2 Content (mEq/L)		9	10	11
Serum Chloride (mEq/L)	124	126	114	117
Serum Sodium (mEq/L)	143	141	135	137
Serum Potassium (mEq/L)	5.6	5.1	4.6→7.0	6.0
Urine Specific Gravity		1.029→1.010	1.010	1.015
Urine Protein (1 to 4+)	4+	4+	4+	3+
Urine Glucose (1 to 4+)	0	Trace	Trace	Trace
Urine Sediment (RBC and WBC per high power field, casts per low power field)	2-4 RBC 15-20 WBC 35-40 granular casts 8-10 hyaline casts	1-4 RBC 2-5 WBC 8-10 granular casts	2-10 RBC 1-8 WBC	1-2 WBC

Results of laboratory studies were essentially like those of the earlier admissions, with the exception that the level for blood urea nitrogen rose to 134 mgm. per 100 ml. and the creatinine level was slightly higher than when studied earlier. The patient remained acidotic and hyperchloremic, and on one occasion the serum potassium rose to 7.0 mEq/L.

Therapy included transfusion of blood and administration of steroids, but this regimen did not effect any significant diuresis and the edema of the extremities remained essentially unchanged.

The patient was admitted for the last time in August 1962 because of persistent edema and dyspnea. Examination showed the blood pressure to be at lower levels than those recorded earlier, the systolic pressure being 160 mm. Hg and the diastolic pressure, 90. No cardiac murmur was now apparent and basal pulmonary rales were apparent. The edema was more extensive than on earlier admissions, involving the scrotum as well as the lower extremities. Staphylococcic furunculosis involved the pubic area. The chief change in results of laboratory studies was a greater degree of anemia. At this time the hemoglobin concentration was 4.2 gm./100 ml. blood.

The pubic furunculosis responded rather poorly to treatment. In the latter part of August 1962, muscular twitching and confusion developed which were followed by a progressively downhill course of the patient. In the last day of life, anuria was noted. Death occurred on September 1, 1962.

Differential Diagnosis

This patient's clinical course was characterized by the nephrotic syndrome, consisting of edema, proteinuria and hypoalbuminemia. The serum cholesterol was at the upper limits of normal. Azotemia was present and the patient was hypertensive. A hypochromic microcytic anemia was present early in the course of his final illness, and apparently became macrocytic by the time of his third admission. Our first knowledge of renal disease in this patient dates back to 1955, seven years before his death. It would be helpful, of course, to know if proteinuria had been discovered previously and whether he had had Bright's disease in the past. The diagnosis of pneumonia in 1957, accompanied by hemoptysis, would immediately raise the possibility of pulmonary embolism, which is further supported by the appearance of thrombophlebitis in the same year.

A disturbing note is the history of urinary symptoms suggestive of a chronic pyelonephritis. The unilateral edema at the time of the first admission is quite noteworthy and would suggest edema on the basis of phlebitis, rather than from the hypoalbuminemia alone. The laboratory findings of the first two admissions are compatible with chronic renal disease. The anemia, which was hypochromic and microcytic, is, in the absence of a history of bleeding, to be considered as part of the renal disease. There is a growing body of evidence that this type of anemia results from decreased elaboration of erythropoietin by the diseased kidneys, although a shortened red-cell survival time in the peripheral circulation has been demonstrated, as well. The findings in the urinary sediment indicate severe tubular dysfunction. The predominance of granular casts would suggest chronic pyelonephritis, although the correlation here is not exact. The hyperchloremic acidosis would indicate rather severe impairment of the renal tubular capacity to elaborate an acid urine, resulting in inappropriate loss in the urine, both of bicarbonate and of fixed base. The specific gravity of the urine, when corrected for the proteinuria, was remarkably low, indicating a loss of capacity for concentration of urine by the renal tubules. These two factors, the inability to elaborate a concentrated urine and the inability to correct a metabolic acidosis, make such patients extremely vulnerable to minor changes in fluid and electrolyte balance. Their equilibrium may be severely compromised by minor events, as an episode of gastroenteritis, which would be well tolerated by a normal individual. The hyperkalemia is a further manifestation of disturbed function in the distal tubule.

In an adult patient without diabetes, the most common cause of the nephrotic syndrome is chronic glomerulonephritis. In this patient, it is interesting to pursue further the fact that the dependent edema was initially unilateral, that the degree of dependent edema seemed out of proportion to generalized body edema and that there had been at least one episode strongly suggestive of a pulmonary embolism. These findings lead one to a consideration of a potentially correctible cause of a nephrotic syndrome, namely, bilateral renal vein thrombosis. This condition may occur as an isolated finding resulting from such diverse conditions as (1) severe infantile dehydration, (2) extension of a primary renal tumor along the renal veins, (3) congestive heart failure, and (4) diffuse vascular disease. It may also occur as an extension from

Continued

thrombosis of the inferior vena cava which, in turn, results (1) from an initial thrombophlebitis in the deep veins of the legs and/or pelvis or (2) from invasion of the inferior vena cava by a pelvic or abdominal tumor. In this patient, an initial thrombophlebitis in the deep veins of the legs, with subsequent thrombosis of the inferior vena cava and renal veins, would very plausibly explain the majority of the clinical findings. Such a diagnosis may be confirmed by phlebography. There are at least two reported cases of renal vein thrombosis in which clinical improvement followed administration of anticoagulants.[1]

In summary, although the nephrotic phase of clinical glomerulonephritis would be the most likely condition in such a patient as the one described, the likelihood of bilateral renal vein thrombosis secondary to thrombosis of the inferior vena cava is an intriguing possibility which should be strongly considered.

Pathologic Findings

At necropsy there was massive edema of the lower extremities, the groin and the scrotum. There were moderate ascites and bilateral hydrothorax. The pericardial sac was obliterated by fibrous adhesions, but there was no apparent constriction of the heart by these. The heart was hypertrophied, weighing 600 gm. The coronary arteries exhibited mild atherosclerosis. Both lungs showed areas of organizing bronchopneumonia. In one lung, there was a peripheral, old healed infarct.

The left kidney weighed 90 gm. and the right kidney weighed 110 gm. The capsules stripped with slightly increased resistance, revealing pale, finely pebbled, cortical surfaces (Fig. 1). In each kidney there were several small cysts, each measuring up to 1.5 cm. The corticomedullary markings were distinct, but the cortex was thinner than normal, measuring about 4–6 mm. The lumen of the inferior vena cava, in the region of the renal veins and just proximal to this area, contained a rather prominent fibrous webbing, characteristic of organized and recanalized thrombosis, causing partial occlusion of the lumen. This process extended into each renal vein with the lumen of the left renal vein more compromised than the right. The major portion of the inferior vena cava, from its origin to the area of the renal veins, was largely uninvolved, but in the right iliac vein there was a fibrous webbing representing old organized thrombosis and similar to the process in the inferior vena cava already described.

Histologically, the kidneys showed marked tubular atrophy with hyalinization of many of the glomeruli (Fig. 2). Those glomeruli which were less severely involved showed prominent diffuse thickening of their basement membranes. Arteries and arterioles showed only minor changes. Stains for amyloid gave negative results.

The renal findings observed are indistinguishable from those of chronic membranous glomerulonephritis. In previously described cases of nephrotic syndrome secondary to inferior vena caval or renal vein thrombosis, diffuse glomerular basement membrane thickening was found in those patients who survived sufficiently long to develop renal changes.[2,3,4] The changes in previously reported cases, however, were not as severe as those seen in this case, and those patients had not survived as long as

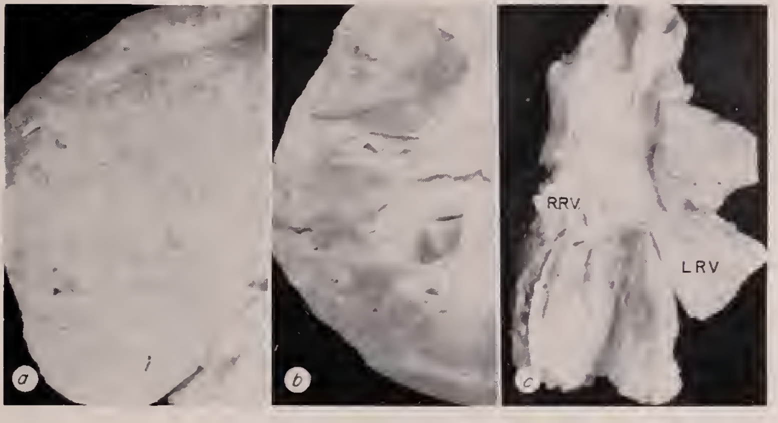

Fig. 1 — *(a)* External surface of portion of kidney. The surface is finely granular. *(b)* Cut surface of same specimen. The cortex is uniformly thin. *(c)* Interior view of inferior vena cava. There is fibrous webbing of the intima of the inferior vena cava and of the ostia of the left (L.R.V.) and right (R.R.V.) renal veins.

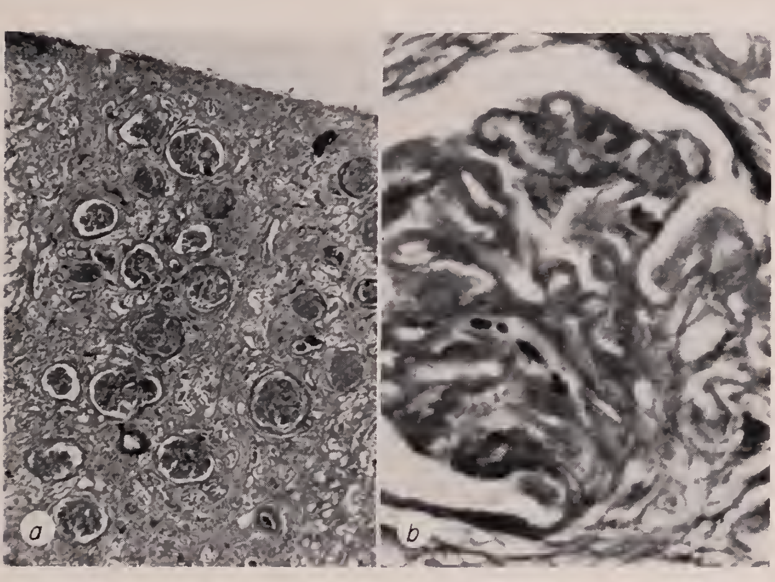

Fig. 2 — Photomicrographs of kidney stained with Mallory-Heidenhain stain. *(a)* Scarring of glomeruli, tubular atrophy and interstitial fibrosis. X 35. *(b)* Diffuse thickening of glomerular basement membrane. X 430.

this patient. Renal vein and inferior vena caval thrombosis has been reported secondary to renal disease of several types, most often amyloidosis, but also in chronic glomerulonephritis, among others.[5] In view of this patient's longer survival from the initial thrombotic episode and presence of incomplete obstruction of the inferior vena cava, it would seem quite reasonable that the severity of the renal involvement may be explained by the caval thrombosis alone, without requiring the assumption of any primary renal disease.

In acute thrombosis of renal veins or of the inferior vena cava, hemorrhagic renal infarction may occur, with rather rapid death. This is a syndrome more common in children.[6] In slower occlusion of the veins,

Continued

the kidneys are first enlarged, and then become atrophied if the patient survives long enough. The first renal change is tubular atrophy and interstitial fibrosis, with later changes involving the glomeruli. The basement membrane thickening appears to be proportional to the length of survival of the patient.

Final Diagnosis

Old thrombosis of renal veins and inferior vena cava with nephrotic syndrome.

Francis B. Tiffany, M.D.,*
Richard P. Lynch, M.D.,*
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Minneapolis, Minn.

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This study was supported by Research Grant #HE-5694 of the National Heart Institute, United States Public Health Service.

Medicare

In commenting on the State of the Union message, Dr. Edward R. Annis, president of the American Medical Association, said that President Johnson apparently had been grossly misinformed by his advisers on the legislation pertaining to Medicare.

Medicare would not be an insurance program of health care for the elderly. It would be strictly a tax program, forcing wage earners to pay a substantial increase in their payroll taxes to finance hospitalization for everyone over 65, including those who are wealthy and millions of others who already are protected with hospital insurance. Testimony of the Chief Actuary of the Social Security Administration shows that every worker earning one hundred dollars or more a week would be forced to pay at least 23 per cent more in payroll taxes to finance this inequitable program. Medicare is unnecessary. Private health insurance, now protecting more than 10 million elderly, is available to those who can pay their own way, and the Kerr-Mills Law, already enacted in more than 40 states, can help those who need help.

Middle Age: When you begin to exchange your emotions for symptoms.
— Irvin S. Cobb

Industrial Medicine

One Aspect of Industrial Eye Care

Ocular hazards in industrial situations have been pointed out for many years, and great strides have been made by industrial safety departments and by compensation insurance carriers. The National Society for the Prevention of Blindness can point proudly to the decline in serious eye injuries brought about by conscientious eye-safety programs and continuous eye-safety instruction.

One aspect of eye care for industrial workers, however, is rarely mentioned outside of ophthalmic literature. This aspect, while not of importance in regard to ocular injury, is most important in regard to ocular efficiency. The time lost from production because of visual difficulty is beyond measure. Despite careful worker placement, in regard to visual demand, the response to a special seeing task changes with time. A 30-year-old worker may perform perfectly a job which is impossible for him when he reaches 45. Production often could be doubled if a worker had proper vision for the task at hand.

Identifying and securing proper eye care for industrial personnel in need can be either routine or impossible, depending on the type of safety program which is followed.

Ideally, the modern approach to the problem would be first to require safety glasses for all personnel and then biennial or triennial re-examination. Some farsighted employers subsidize a portion of the cost of the examination and the entire cost of safety glasses, and undoubtedly they are repaid several times over by increased efficiency, co-operation, and attendance, and also by decreased loss of time from eye accidents.

The loss of accommodation of the eye increases gradually from childhood. One usually reaches the early or mid-forties, however, before the effect is noticed, and then only for fine, detailed, near work. Nevertheless, increased effort is required for all close tasks even before the blur of print makes the onset of presbyopia known. This increased effort results in fatigue, and fatigue results in poor performance. Periodic eye examination can detect this accommodative loss, and prescription of proper lenses for the employee's specific task can be recommended.

The testing of vision by members of the safety department or by attendants in the first-aid room has no place in this program. A 20-year-old person may have normal 20/20 vision but may be compensating for enough hyperopia to make him unfit for any task which requires use of the eyes for any close work.

Ocular muscle imbalance also is an important source of discomfort and, in some instances, may make the use of the eyes for prolonged near tasks next to impossible. Hyperopia and astigmatism are the chief causes for so-called eyestrain, which frequently results in poor concentration, inefficiency, headache, and the like. If one relies on testing of distant vision alone, these cases will remain unidentified, for accurate determination of the refractive error of the eyes frequently can be determined only by refraction during induced cycloplegia. Pre-employment eye examination often could result in more advantageous placement were personnel officers acquainted with the findings of such examination and if an ophthalmologist's recommendation on use of the eyes were sought.

(Continued)

The use of multifocal lenses by elderly workers is one of the most commonly ignored, yet one of the most satisfying, procedures that can be employed. The ordinary bifocal lenses will enable one to see well across the room and at a reading position, but a conventional trifocal is needed for seeing at these distances and at arm's length. Trifocal lenses with one segment in the top of the lens is the solution for most problems where near vision overhead is necessary. Segments of various sizes are available in strengths that can satisfy any special visual problem once the problem is identified. Many a worker will go on for years, feeling for overhead screw slots and the like, without ever knowing that there are available lenses with which he could see what he is doing. When one employee in a plant is given a prescription for special occupational multifocal lenses, it is surprising how many fellow workers realize that they have similar visual problems and that specialized solutions for these problems do exist.

As the worker becomes older, accommodation becomes even more inelastic; therefore, the range of clear vision becomes more limited. This means that a regular prescription for bifocals may serve well if the job happens to involve work at a reading distance and position; but if the work is fine and delicate the working distance may be much closer than the normal reading distance of about 14 inches. Then a different prescription obviously is indicated.

As in the field of transportation an anomalous situation is present in most industrial applications: The young worker with the most adaptable eyes and keenest vision does work with little visual demand, while the older person, because of accumulated experience, draws the job that is most exacting on his eyesight, which by this time has lost most of its adaptability.

Usually it is not necessary for a safety engineer or a job analyst to look for situations where visual demand is not being met with visual performance. A routine eye examination where the worker is free to discuss his visual needs usually will suffice. By observing fellow workers, the employee becomes educated to the fact that special seeing tasks require special optical consideration.

Periodic eye examination is also important in preventive medicine; for systemic disorders, and incipient glaucoma, cataract, or other conditions may be discovered by this means.

Theodore G. Martens, M.D.
Committee on Industrial Health
Minnesota State Medical Association

Study of a Remarkable Anti-Inflammatory Agent (Cucumase)

Cucumase has been found to be of great value in the following conditions: traumatic wounds of all kinds, phlebitis, hemorrhoids, sore toes, sore holes, sore heads, sinusitis, bronchitis, thrombophlebitis, postprandial belching, incarcerated flatus, and a host of other conditions considered to be too embarrassing to mention.

Administration

Cucumase has been prepared for administration by the following routes: oral, sublingual, parenteral, and topical. In addition, it can be given by nebulization, enema, as eye drops, nose drops, and finally as a suppository (in the form of a small cucumber, of course).

P. Ciaglia, M.D.
Consultant Latrogenic Metaphysics
Utica, N. Y.

JAMA, Feb. 22, 1964.

Grand Rounds

Hypertrophic Gastritis

Chronic hypertrophic gastritis was first described by Menetrier in 1888. He described this condition as appearing mainly in two forms:

1. Polyadenoma "polypeaux" occurring as multiple polypoid adenomatous lesions affecting the gastric mucosa diffusely and showing numerous mucous cysts.

2. Polyadenoma "en nappe" — a localized, well-demarcated plaque composed of hypertrophic mucous membrane without lobulations and without mucous cysts.

Synonyms found in the literature for this condition include Menetrier's disease, giant hypertrophy of gastric mucous membrane, and adenopapillomatosis gastrica. .

Incidence

It is estimated by Fieber that hypertrophic gastritis comprises 18 to 57 percent of the cases of chronic gastritis and is thought to occur in about 6 percent of the general population. Yet there was a total of only 63 reported cases as late as October, 1959, which had pathologic verification of giant hypertrophic gastritis.

The condition has been found in all ages between 29 and 76. One three-year-old patient, diagnosed as having "idiopathic hypoproteinemia," also had large gastric rugal folds.

Estimates of frequency vary from equal distribution between sexes to a 3:1 male predominance.

Etiology

The etiology of this condition is mere speculation; there are very few common denominators in its history. Irritants, vitamin and dietary deficiencies, mechanical factors, and endocrine factors have been implicated.

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*Medical Grand Rounds, Mt. Sinai Hospital, Nov. 13, 1962.

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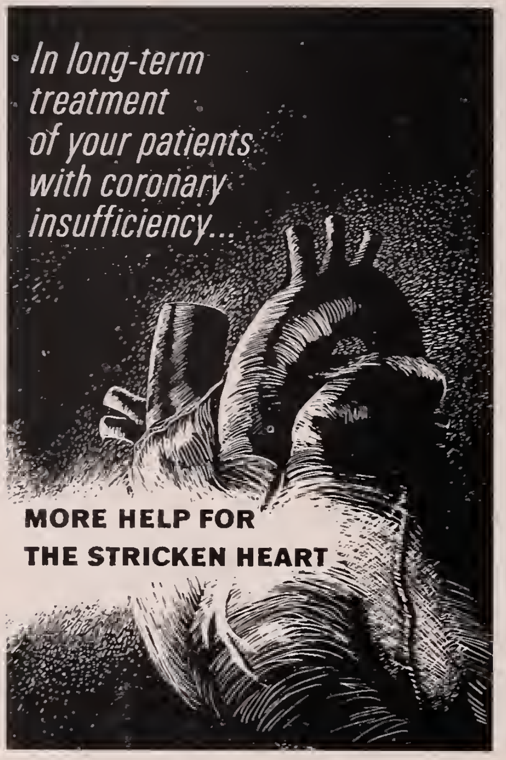
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Symptoms

There is no distinctive syndrome for hypertrophic gastritis, but there does appear to be a general pattern for the symptomatology.

In an analysis of 50 proven cases Fieber reported pain as the cardinal symptom, occurring in 74 percent of the cases. He found that the pain was like that of a peptic ulcer. It was usually localized in the epigastrium, had a tendency to occur one to two hours after meals, and was usually relieved by food or alkali. Of the six cases reported by Moran et al., two had sharp epigastric pain; one had a "beating sensation" in the epigastrium; one had diffuse upper abdominal discomfort of ten years' duration; the other had no pain. The frequency of other symptoms reported by Fieber was:

weight loss — 60 percent of the cases
hemorrhage — 20 percent
vomiting — 42 percent

In some cases the vomiting was presumably caused by intermittent redundant gastric mucosa through the pylorus. This phenomenon was earlier demonstrated at surgery by Eckhoff.

Physical examination was generally unremarkable with the exception of occasional epigastric tenderness or palpable abdominal masses.

Peripheral edema was occasionally observed, associated with hypoproteinemia and in the absence of cardiorenal disease.

Laboratory

Serum Protein

At the time of Moran's article in 1959, serum proteins had been measured in only seven cases, four of which had decreased serum protein levels. There are several hypotheses for the association of hypoproteinemia and edema with hypertrophic gastritis: (1) deficient protein intake secondary to the basic disease; (2) toxic suppression of protein formation by some factor produced by the disease mucosa; (3) loss of serum protein from the gastric mucosal surface.

In support of the latter hypothesis is the work of Citrin et al. using I^{131} labelled albumin. Their subject had a remarkably accelerated turnover of albumin compared to normal control subjects; also they found that the gastric juice contained large amounts of albumin, accounting for almost half of the patient's daily loss.

Hypoacidity

An associated hypoacidity has also been reported. In 1955 Kenney et al. reported that anacidity after histamine was present in 17 of 30 cases tested among the 45 cases of hypertrophic gastritis then in the literature. The achlohydria may be due to replacement of the acid-secreting cells by the proliferative mucosa. In one series of patients with adequate parietal cells on histological examination, an abundance of free hydrogen chloride was present.

Blood and Urine

CBC and urinalysis are normal except in cases where hemorrhage has occurred.

Continued

Radiologic Changes

Fieber cites only two correct radiological diagnoses in 50 cases of giant hypertrophic gastritis that were established by surgery. The markedly distorted rugal pattern usually leads to the radiological diagnosis of gastric malignancy or lymphosarcoma. It may also be confused with multiple polyposis, Hodgkin's disease, and syphilis.

The hypertrophy is most frequently found in the mid-portion of the stomach along the greater curvature, though the entire stomach may be involved. Multicentric erosions and superficial ulcerations may be present.

At fluoroscopy, in the study of six cases by Moran, the stomach was found to be of medium size and in four cases to possess normal peristaltic activity. None showed evidence of rigidity or absence of peristalsis. This finding contrasted with the discovery of filling defects or polypoid masses which occupied a significant portion of the stomach.

Thus the diagnosis of giant hypertrophic gastritis may be strongly considered when there are continuous folds or polypoid mucosal lesions in the absence of rigidity and in the presence of peristalsis. However, the radiological appearance of this abnormality is not sufficiently distinct from neoplasia to establish a clinical diagnosis.

Gastroscopy

Gastroscopy has been only slightly more successful than radiology as a diagnostic tool. In the 26 patients subjected to gastroscopy before October 1959, only eight had been correctly diagnosed. Various types of neoplasms were diagnosed in the remaining cases, only to find hypertrophic gastritis at surgery.

Pathology

The gross appearance of the stomach and the sensation to palpation will usually suggest hypertrophic gastritis.

In the "en nappe" type, gastric rugae are thicker, sulci deeper, and contour more tortuous than normal. A similarity to cerebral convolutions has been noted. Adjacent lymph nodes are usually enlarged. Tactile sensation has been described variously as "a bag of worms," "full of sausages," and "varicocele."

Attempts have been made to distinguish the two types of hypertrophic gastritis histologically.

Hyperplastic Type

"Polypeaux" designates the hyperplastic phase. There is an abnormal increase in glandular elements but not in the connective tissue elements. The microscopic picture is one of rapidly growing glandular cells with occasional mitotic figures. The epithelium is modified into various forms but is always laid down in a regular manner. The basement membrane is preserved, and proliferating cells never pass beyond it.

There is a decrease or absence of parietal and chief cells. Patches of intestinal metaplasia may be present, recognizable by the presence of a striate border and of Paneth and goblet cells forming the bases of new tubules. Attempts have been made to correlate the histological findings with the anacidity sometimes observed. Proponents say that the Paneth and goblet cells become predominant with consequent lessening of parietal cell activity and less acid secretion. However, a correlation has not always been found to exist.

Cystic dilatation of gastric glands is encountered in the "polypeaux" type and connotes nothing more than the existence of some occlusive mechanism in the drainage system of a gland.

Hypertrophic Type

"En nappe" designates the hypertrophic type, where there is an abnormal increase in the thickness of the stomach wall as the result of the enlargement in size of the gastric glands and also interstitial connective tissue.

Hypertrophy of the interstitial connective tissue is characterized by increased cellular infiltration and edema. Moderate to severe vascular congestion is found in almost every case. The cellular infiltrate consists mostly of lymphocytes and reflects the presence of inflammation which is thought to be nonbacterial in nature.

Treatment

Medical treatment is the therapy of choice in the various forms of uncomplicated hypertrophic gastritis, but it is wholly empirical in nature.

Medical Treatment

1. Usual dietary precautions advised in treating peptic ulcer.
2. Avoidance of alcohol and other mucosal irritants.
3. Replacement therapy to offset the effects of diminished hydrogen chloride excretion and to combat hypoproteinemia when present.

Surgical Treatment

Many believe the indications for surgery are the same as those for peptic ulcer: repeated or massive hemorrhage, obstruction, intractable pain, or possible malignant change.

Bartlett and Adams have advocated total gastrectomy for diffuse involvement. Fieber has recommended partial gastrectomy because of the unpleasant symptoms and adverse nutritional effects which have followed total gastrectomy.

In the cases reported prior to October, 1959, total gastrectomy was performed in 13, partial gastrectomy in 46, and gastrotomy, with or without biopsy to rule out malignancy, in 17. Follow-up data available in 18 of the 46 patients with partial gastrectomy shows satisfactory results with weight gain in 13.

Course

Duration of symptoms has varied from two months to 22 years, with an average duration of two years.

Strode says it is strongly suggested but not established that gastric hypertrophy may dispose to malignancy. At least six cases of hypertrophic gastritis have been associated with invasive adenocarcinoma of the stomach. As in so many other aspects of this condition, there remains room for doubt.

(Continued)

Case Report

The patient was a 57-year-old white female housewife who entered the hospital on 10-19-'62 with the history of a 30-pound weight loss over the previous year and a 30-day complaint of anorexia, nausea and vomiting.

Physical Examination:

This showed a thin, elderly woman with blood pressure of 150/100, pulse 80, respirations 20, and temperature of 97.2. A questionable small mass in the epigastrium was the only positive physical finding.

Laboratory Examination:

Hemoglobin on admission was 12.9 gm%; WBC 4,400; 62% neutrophils; 35% lymphocytes. Urinalysis was negative; stool guaiac 1+. Gastric analysis showed 7% free acid with the fasting specimen and 90% after histamine stimulation. Serum proteins totaled 6.7 gm% with an A/G ratio of 4.5/2.2. An upper GI series on 10-9-'62 in the Outpatient Department revealed multiple filling defects in the antrum of the stomach, some of which were due to giant folds with associated entrapment of barium. There was suspicion for ulceration on both the greater and lesser curvature aspects of the antrum. Duodenal bulb distortion was also questioned.

It was generally felt that the patient had a gastric carcinoma or lymphosarcoma, and surgery was recommended. An exploratory laparotomy was performed on 10-29-'62. The stomach was grossly within normal limits. A gastrotomy incision was made. One large ulceration just proximal to the pylorus was found. Vagotomy and 50% gastrectomy were then decided upon. The pathology report showed benign gastric ulcer and hypertrophic gastritis. The postoperative course was uneventful and the patient was discharged on 11-7-'62.

John Godes, M.D.
Mt. Sinai Hospital

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Think not of yourself as "the architect of your career" but as the sculptor. Expect to do a lot of hard hammering and chiselling and scraping and polishing.

— Forbes Epigrams

In this work, when it shall be found that much is omitted, let it not be forgotten that much likewise is performed. — Samuel Johnson

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If all the world is wrong reform yourself.— C. O. R.

Abstracts, Briefs and Commentaries

A NEW TREATMENT FOR PARALYTIC ILEUS

The concept of electrical stimulus, or pace-making, in the treatment of heart block has been adapted to the treatment of abdominal distension due to inadequate peristalsis. They found that a current of 7 to 10 M.A. at a frequency of 50 cycles per second, given for 5 to 10 seconds, could induce effective peristaltic activity. A unipolar transluminal stimulation was employed by introduction of an electrode through a nasal suction type catheter inserted either into the antrum or into the first or second duodenum. In these areas stimulus was found most effective. However, the rectal route of stimulus was also found of clinical usefulness.

Forty patients with paralytic ileus of differing etiologies were treated with very impressive results. Several cases are described, including rather extensive surgical manipulation of the abdominal viscera. An average of 16 hours of pacing in the postoperative period was followed by passage of flatus and the first stool. During periods of pacing the patient could experience stomach rumbling, bowel sounds were obviously audible when examined by stethoscope, and activity could be observed directly by fluoroscopy. Further studies on animals and on patients during operation revealed unquestionable response of the bowel to electrode stimulation.

Dog experimentation revealed more forceful peristaltic activity in response to pacing when the stomachs were partially filled with liquid.

Abstractor's Comments: The very significant advantages in terms of more simple and safe postoperative clinical course are quite obvious benefits of this important discovery. It is this reader's opinion that gastrointestinal pacing may shortly be considered as the most significant advancement in clinical management of intestinal distention since the development of nasogastric suction. Surgeons, in particular, will be duly grateful.

J. H. Strickler, M.D.
Minneapolis, Minn.

Bilgutay, Aydin M., Wingrove, Robert, Griffen, Ward O., Bonnabeau, Raymond C., Jr., and Lillehei, C. Walton: "Gastro-Intestinal Pacing — A New Concept in the Treatment of Ileus." — Ann Surg 158:338, Sept. 1963

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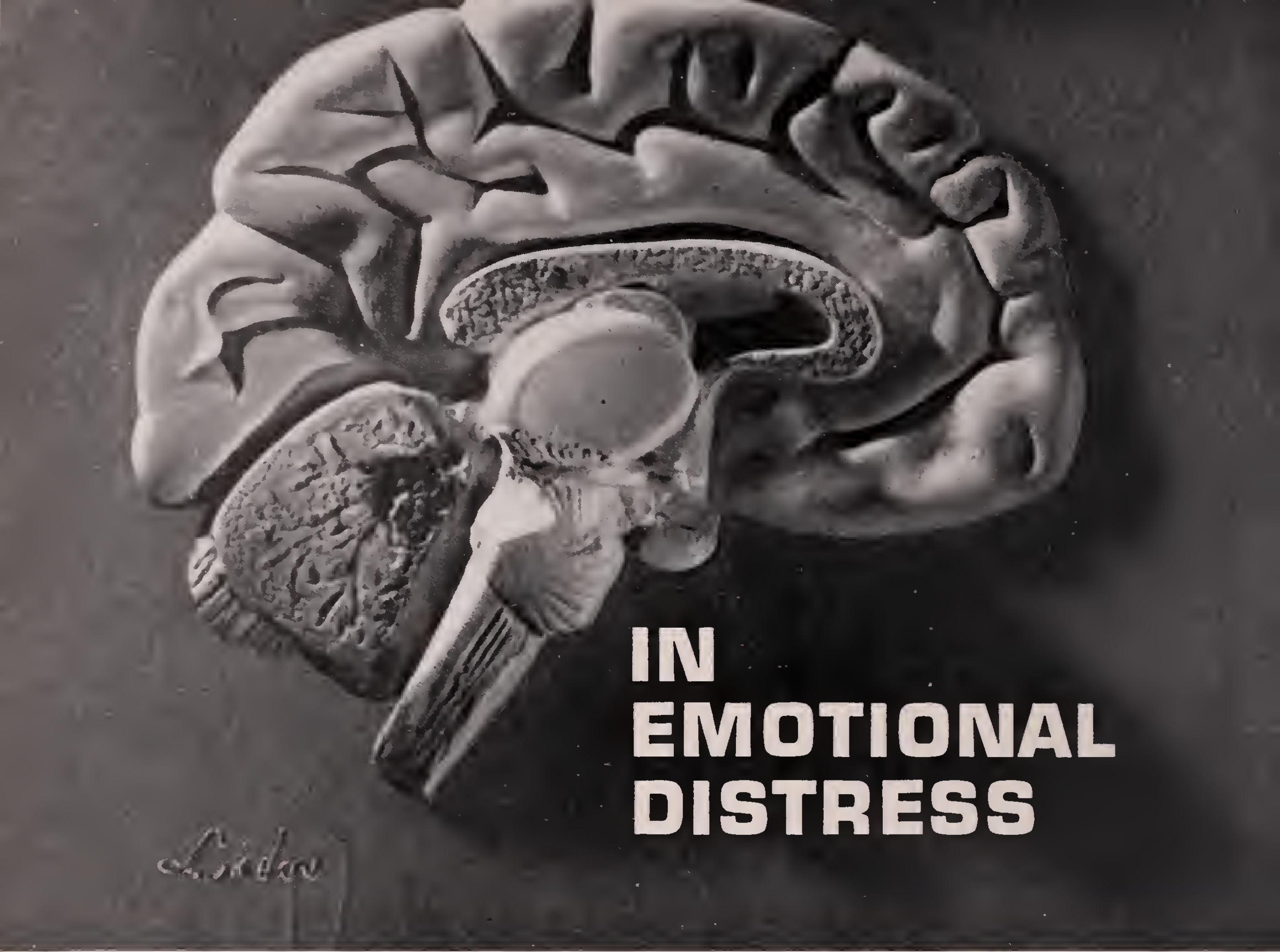

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Usual adult dosage: One 400 mg. capsule or two 200 mg. capsules at breakfast; repeat with evening meal.

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CME-1969

WALLACE LABORATORIES *Cranbury, N. J.*

C.I.O.M.S. SEMINAR ON HOSPITAL INFECTIONS, LONDON, ENGLAND

The author summarizes the International Seminar on Hospital Infections held by the Council for International Organizations of Medical Sciences. There were delegates from twenty-six countries and the World Health Organization. There were 111 delegates, 57 of whom were from the United Kingdom and 52 from other countries. All were experts on some aspect of hospital-acquired infection and each represented his country and a scientific medical organization.

Brief summaries by various leaders in the field are given by the author. Basically, the seminar demonstrated the lack of knowledge in many areas of hospital infections. This included designs of hospitals, the wards, the central supply units, and the operating rooms. The factors of exogenous contamination by visitors and hospital staff, patients with infected wounds as well as the endogenous contaminations from the patients themselves, i.e., respiratory, vaginal, and urinary tract; and gastrointestinal tract contamination with spread throughout the hospital wards was discussed. Also the factors of resistance of the individual host, carriers, and patients exposed to infecting agents. The most prevalent bacteria was the Staphylococcus aureus, but other bacterias of growing importance were the pseudomonas aeruginosa and the anaerobic bacteria. In general, it seemed to be the feeling that the medical patient with infection was a more serious threat to the other members of the patient load than carriers. An interesting fact, also, that cropped up in the many discussions was the fact that individuals with skin diseases seemed to be a more potent source of infection than acutely infected wounds. Sterilization procedures, ward designs, bed linens, laundry chutes, etc. were discussed and again demonstrated the need for further clinical study.

The author concludes by saying there were "many voids evident in our knowledge and the incomplete and inadequate status of related scientific information emphasizing the importance of developing an intensive, imaginative, and sustained research program for the solution of problems of hospital acquired infections."

Although this article does not describe many areas in detail it gives the clinician a good over-all summary of the conclusions of individuals and the problems that are involved.

Jerome T. Grismer, M.D.
Minneapolis, Minn.

Altmeier, W. A.: Surg 54:419, Sept. 1963

PAIN IN MULTIPLE MYELOMA

Seventy-two patients with multiple myeloma were surveyed with respect to the causation of pain. Almost all those who had had an abrupt onset of pain showed a fracture at the site of pain. About one half of those with a gradual onset also had a fracture. The great majority of osteolytic lesions were painless. The relief afforded by local irradiation, which could not have been due to healing of the fracture, may have been due to an effect on extruded tumor tissue.

Courtesy of References and Reviews
Journal of the American Medical Association

Whitelaw, D.
Canad Med Ass J 88:1242 June 22 1963

Continued

PERITONEAL FLUID PH AFTER PERFORATION OF PEPTIC ULCERS

In the authors' opinion, the signs of an acute perforation of a peptic ulcer were not secondary to an "acid peritonitis." This opinion is based on their analysis of the Ph of the peritoneal fluids in 59 patients who had an acute perforation of the peptic ulcer. Fluid was taken at the time of laparotomy as soon as the peritoneum was incised. In 58 of these cases the peritoneal fluid was alkaline. The authors then cited laboratory research work which demonstrated that dilute hydrochloric acid is rapidly neutralized when injected intraperitoneally in amounts of 15 mm. per kilogram of body weight. Another possibility is that the acute perforation stopped the secretion of acid by the stomach. Although the authors felt that the initial fluid at the time of perforation was undoubtedly acid, the intraperitoneal mechanism rapidly neutralized the acid and "board-like rigidity" of the abdomen or wall usually found several hours after perforation was not due to acid peritoneal fluid.

Jerome T. Grismer, M.D.
Minneapolis, Minn.

Howard, J. M., Singh, L. M.: AMA Arch Surg 87:141-142, Sept. 1963

DETROIT POST OFFICE SURVEY FOR CHRONIC RESPIRATORY DISEASE

One thousand five hundred eighty-four men and women over age 40, all working in the Detroit Main Post Office, have been surveyed for chronic respiratory disease by means of a standard questionnaire, screening ventilatory test, and a Mobile Unit X ray of the chest. General urban environment for home and work were similar throughout the group, which was about equally Negro and white. Some of the problems and pitfalls of interviewer training, pulmonary function testing, and data analysis are presented. Results to date indicate that symptoms and signs of chronic respiratory disease affect more than 30% of this otherwise normal working population; that they are about equally divided in frequency between whites and nonwhites; and that some appear to be more common among men and others among women.

E. Osborne Coates, Jr., M.D.
George C. Bower, M.D.
Henry Ford Hospital
Detroit, Michigan

CARCINOMA OF PROSTATE

A mixture of estrogen, triethylenemelamine, cortisone, and antibiotics was injected directly into the tumor of 37 men from 55 to 85 years of age with prostatic carcinoma. The injections, which require local anesthesia only, were repeated every four to eight days for six weeks. There were no untoward effects. At the time of writing, twenty-nine patients were still alive and with one exception had shown improvement. All gained weight. In patients having shown dilatation of the urinary tract, regression was obtained. Some kidneys, apparently functionless, returned to normal. Most prostates were reduced in size and nodularity, in some instances to a point that encouraged surgical removal.

Courtesy of References and Reviews
Journal of the American Medical Association

de la Pena, A.:
J Int Coll Surg 38:312 Oct. 1962

ACUTE ILIOFEMORAL VENOUS THROMBOSIS

After thrombectomy on 45 patients at the University of Louisville Hospital, the authors have found excellent results in the majority of patients provided the procedure is done in less than 10 days after onset. The diagnosis of iliofemoral thrombosis is made with certainty only when a massive edema of the leg from toe to groin is present with tenderness along the femoral canal.

The authors employed local anesthesia and considered this to be mandatory so that the patient could strain down during extraction of the clot in order to decrease the possibility of pulmonary embolization. The usual heparinization was employed. The incision apparently was located over the upper portion of the femoral vein and did not extend upward to expose the common iliac in a direct fashion. It was found that 10 to 14 days after the acute thrombosis complete extraction of the clot was difficult or impossible. Therefore, a much less satisfactory result was obtained in the later periods.

Thirty-four patients had symptoms of occlusion of less than 10 days duration, with 26 cases resulting in apparently normal legs. Eighty-three percent of the 65 percent of the total group which had postoperative venograms had normal venous systems.

The authors emphasize the importance of thrombectomy as a means of offering the patient an excellent opportunity of escaping the postphlebitic limb problem resulting from incompetence of the deep thrombosis.

J. H. Strickler, M.D.
Minneapolis, Minn.

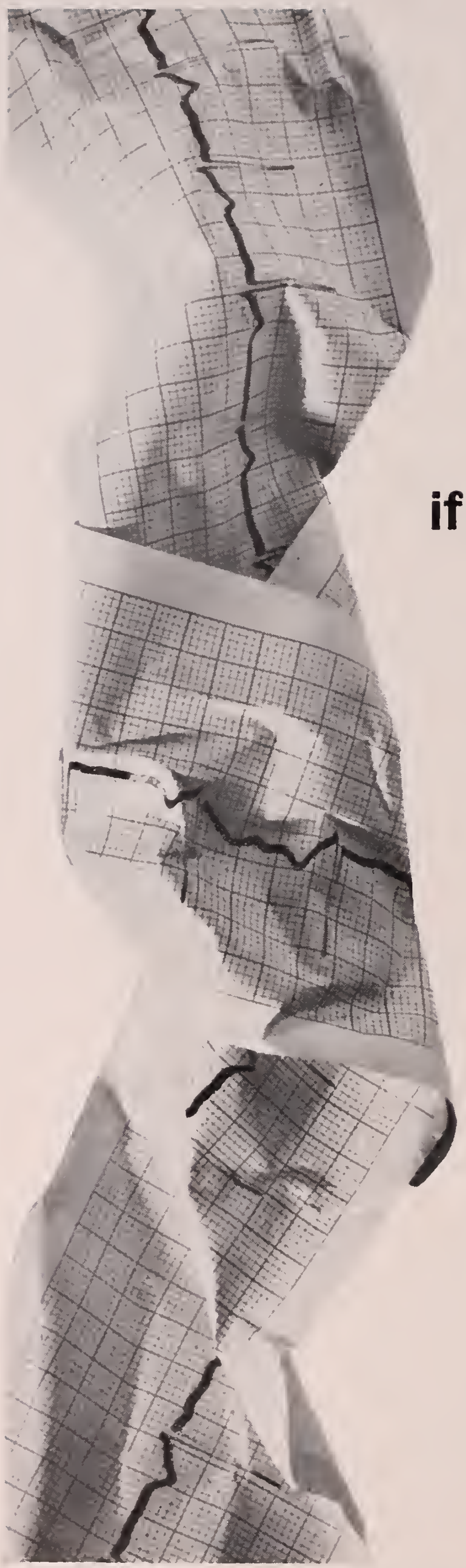
Haller, Alex J., Abrams, Berell: Use of Thrombectomy in Treatment of Acute Iliofemoral Venous Thrombosis in 45 Patients. Ann Surg 158:561 Oct., 1963

DEFORMITIES OF THE ANTERIOR WALL OF THE CHEST

The most common anomalies of the anterior portion of the chest belong to the chondrosternal depression (pectus excavatum) or to the chondrosternal prominence (pectus carinatum). The authors felt that these deformities are not harmless anatomical variants, but are physiologically and psychologically crippling deformities. The basic defect is from an overgrowth of the costal cartilages. In their technique of repair, they made the following steps: (1) The sternum should be adequately mobilized, its abnormal angulation being corrected by transverse osteotomy, (2) bilateral and adequate removal of the involved costicartilages would be essential, and (3) the corrected position of the sternum should be secured by using the patient's own living tissue undeprived of its blood supply as an internal support. A convexed transverse incision would be utilized in most cases. In the pectus excavatum repair, the xyphoid process should be placed into a retrosternal position which maintained the slight overcorrection of the sternal body.

The authors also described methods of handling rotation of the sternum, chondrosternal prominence or pectus carinatum and chondromanubrial prominence with chondrogladiolar depression.

Continued



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Two hundred and twenty patients were operated upon without a death. The authors could not determine objective disability of the disease by pulmonary function of hemodynamic study. However, they noted that the breathing of most patients improved and the chest walls became more mobile with larger inspiratory and expiratory excursions and absence of the paradoxical motion of the involved area. Young children improved physically and mentally; respiratory infections and asthmatic attacks disappeared completely. The psychological benefits were among the most important aspects of the surgical repair.

In the author's opinion, the optimum time for operation was between two and six years of age. However, they also indicated that older patients with severe deformities would respond satisfactorily to surgery.

This is, indeed, a very difficult decision for the physician and the family alike. However, further comprehensive objective data of the physiologic changes are needed in this deformity to prove whether the functional disability exists as the authors claim.

Jerome T. Grismer, M.D.
Minneapolis, Minn.

Sanger, P. W., Taylor, F. H., and Robicsek, F.: "Deformities of the Anterior Wall of the Chest." SG&O 116:515, May 1963

LEUKOCYTE ALKALINE PHOSPHATASE AS A CHROMOSOME MARKER

It has been demonstrated that in Mongolism there are 47 chromosomes in contrast to the normal 46. The extra chromosome is one of the small acrocentrics, probably associated with pair 21. In chronic myelogenous leukemia, there is also a chromosomal abnormality consisting of a deletion of the long arm of one of the pair designated as number 21. Since the polymorphonuclear leukocytes in chronic myelogenous leukemia are known to be deficient in alkaline phosphatase, it is hypothesized that the deleted portion of chromosome 21 carries the gene determinant for alkaline phosphatase, and, furthermore, that trisomy of this chromosome (as in mongolism) might lead to increased levels of leukocyte alkaline phosphatase. In a study of 58 Mongoloid children, it was found that up to the age of 10 the polymorphonuclear leukocytes did differ from controls as regards alkaline phosphatase, being higher than the controls. After the age of 10 the difference could not be established. Although the effect of aging was not understood, the evidence is interpreted to mean that leukocyte alkaline phosphatase is controlled by a gene on chromosome 21. As such, this would be the first reported incidence of any autosomal (non-sex-linked chromosome) marker. There are, of course, many sex-linked inheritable patterns on the sex chromosome.

Robert A. Green, M.D.
St. Louis Park Medical Center

Alter, A. A., Lee, S. L., Pourfar, M., Dobkin, G.: Studies of Leukocyte Alkaline Phosphatase in Mongolism: A Possible Chromosome Marker. Blood 22:165, August 1963

Continued

CIRCULATING CANCER CELLS

For more than a century the blood stream has been regarded as the route of spread to distant organs. The authors discuss the question of blood-borne cancer cells. They divide the subject into three parts: 1. How many cells are released. 2. How many of the released cells became metastases. 3. What factors determine successful implantation.

It is pointed out that the conclusions drawn from animal research may not apply to humans.

From the laboratory of histology and pathology, the authors have drawn conclusions aided by the findings in 100 autopsies in deaths from pulmonary carcinoma. Although the kidneys are small, they estimate that there are between two and three million glomeruli with 37 miles of capillaries. Only minimal amounts of blood are bypassed. The kidneys seldom show metastases and even if they do the glomeruli persist.

In 100 autopsies in which the patients died of pulmonary carcinoma, twelve were found with kidney metastases. A comparison of the metastases to other organs is made in the group with metastases in the kidneys and the group that had no metastases. The authors attempt to develop an index of metastases from these findings.

Because lung circulation drains directly into the left heart, pulmonary carcinoma affords an incomparable opportunity for showering cancer cells into the body. In spite of the millions of cells freed into the blood stream, few are trapped by the kidney or other organs. The authors pose the question as to where these cancer cells are lost and suggest that the blood stream itself may contain certain factors that determine their fate. It is further suggested that the lymphatic system is also a field for further study and research in an effort to determine the fate of circulating cancer cells.

Author's note:

This article impressed me greatly as I started to review it. The more I read it the more I became confused by the part played by the index explanation. The seeming immunity to invasion of the kidney and the apparent filtration of cancer cells through the kidney as well as through other organs suggest that many of the cancer cells are already dead, or that some factor causes live cells to implant. A goodly number of cancer cells are demonstrable in the veins as they leave the organ of primary invasion.

Stanley R. Maxeiner, Sr., M.D.
Minneapolis, Minn.

Onuigbo, Wilson J. B. and Glasig, M. B.: An Index of the Fate of Circulating Cancer Cells. Lancet (London) Oct. 1963.

Character is pretty much like window glass — when it is cracked, it is cracked both inside and out. — Voice of Calvary Tabernacle

BOOK REVIEWS

MAN AND HIS FUTURE — **Gordon Wolstenholme, Little, Brown and Co., Ltd. Boston and Toronto, 1963**

The book, "Man and His Future," contains a collection of essays designed to appear together, each one followed by a discussion by several contributors very much in the style of the old CBS "Invitation to Learning Series."

The range of ideas is very wide, since the variety of scientific disciplines is by no means limited to biology and medicine. D. M. MacKay's chapter on "Machines and Societies" raises many of the problems encountered by a physicist entering the much different discipline of biology.

Such stimulating writers and brilliant thinkers as Biologist Julian Huxley; Biochemist and Geneticist J. B. S. Haldane (son of the eminent physiologist); Anthropologist Carleton Coon; Nobel Prize Physiologist-Chemist Albert Szent-Győrgi; Geneticist Joshua Lederberg; Biologic-Psychiatrist Hudson Hoagland; and Mathematician and Philosopher of Science, J. Bronowski, present speculations upon our future fate that captivate the imagination.

In some areas the review of or establishment of background appears a bit profuse. However, in other sections the abandon of "Brave New World" pervades more than precise science.

The reader will be entertained by many catch statements such as that of Hudson Hoagland in his chapter, "The Potentialities in the Control of Behavior": "The fate of man has become the prize in a grueling race between education and disaster," or one by Joshua Lederberg: "No one who has known the children of accepted geniuses would suppose the population would greatly benefit by there being several hundred of them."

The book represents, at least in part, an objective, philosophical contemplation of the future by some of the more active and competent minds of this period. I would recommend that its reading be undertaken when one has adequate time for thoughtful study and contemplation.

J. H. Strickler, M.D.
Minneapolis, Minn.

ATLAS OF BONE TUMORS — **W. S. Gilmer, M.D., G. B. Higley, M.D., W. E. Kilgore, M.D. C. V. Mosby Co., St. Louis, 1963. Price $27.50**

This beautifully prepared atlas on bone tumors deals with 25 distinctly different types of bone tumors. The clinical characteristics of these bone tumors are briefly described and each one is illustrated with colored photographs, X rays, and beautifully reproduced histologic sections in color.

Reading references are adequately detailed in the appended bibliography, each chapter being indicated separately. The index is adequate.

The book is beautifully bound and edited, and the uniformity of its format and illustrations make it pleasurable reading.

This should be a very valuable book for students, pathologists, roentgenologists, surgeons, and orthopedists.

Carl O. Rice, M.D.
Minneapolis Minn.

MARGIN OF SAFETY — **John Rowan Wilson. Doubleday and Company, 1963. 258 pages. $4.95**

"Margin of Safety" is an informative story of the development of vaccines for the prevention of poliomyelitis. The author, a doctor, had first hand information concerning the problems connected with the ultimate preparation of the vaccines. John Rowan Wilson has the skill of a writer and the insight of a scientist. The result is a fascinating account of the race to produce a successful vaccine. The participants: men, companies, foundations and governments, are dealt with in a vivid but critical manner. The book can be recommended.

F. W. Hoffbauer, M.D.
Minneapolis, Minn.

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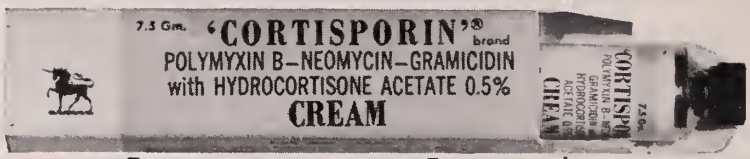
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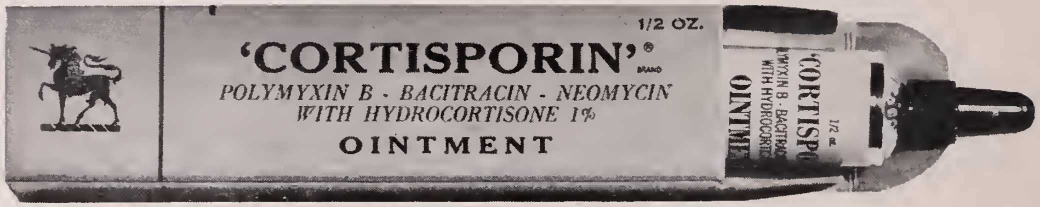
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Special Articles

Maternal Deaths Due to Trophoblastic Tumors

MELVIN P. BAKEN, Jr., M.D.*
Minneapolis, Minnesota

THE MINNESOTA State Maternal Mortality Committee has directed a statewide study of all maternal deaths since April 1, 1950. Analysis of each individual death connected with pregnancy, childbirth, and the puerperium for three months postpartum has been carried on continuously since that time. This study is supported by the Minnesota State Medical Association and the State Board of Health in an effort to bring about a reduction in preventable deaths. Complete records and carefully prepared statistics have been kept of these cases for use in reporting the various causes and types of maternal deaths.

There were 549 maternal deaths from all causes in the State of Minnesota between April 1, 1950, and March 31, 1962, a period of 12 years. Three hundred and twenty-four of these were considered obstetrical deaths. During this same period the State Board of Health reported 993,263 live births, giving an over-all gross maternal mortality rate of 0.55 per 1,000 live births and the corrected over-all maternal mortality rate of 0.33 per 1,000 live births. During the last year of this series (1961) there were only 27 maternal deaths from all causes — 17 of which were obstetrical. The gross maternal mortality for that year was thus 0.31 per 1,000 live births and the corrected maternal mortality rate 0.20 per 1,000 live births.

The reporting of maternal deaths is required of every hospital and accordingly is the first notification received by the Health Department in most cases. Other cases are discovered through death certificates, cross-matching of birth certificates with death

TABLE I
Choriocarcinoma Deaths Per Year

Year	Live Births	Choriocarcinoma Deaths
1950	76,074	1
1951	80,099	2
1952	78,990	1
1953	79,362	1
1954	83,033	0
1955	81,665	1
1956	82,620	2
1957	86,019	2
1958	85,594	1
1959	87,724	2
1960	88,126	1
1961	85,954	0

Population of Minnesota — 3,413,864 (1960 Census)

Continued

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*From the Minnesota Maternal Mortality Committee.

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certificates, newspaper reports, etc. An obstetrician investigator is then assigned to the case; he examines the hospital records, interrogates the attending physician and other medical personnel involved in the case, and prepares a summary which is presented to the members of the Maternal Mortality Committee for final judgment as to the diagnosis, management of the case, and preventability. All deaths in the State of Minnesota due to trophoblastic tumors are included in the maternal mortality series as one category of maternal deaths.

Choriocarcinoma

The trophoblastic tumor deaths comprise the cases used in this report. Over the 12-year period, there were 14 deaths due to choriocarcinoma and/or chorioadenoma destruens, approximately one fatality for every 70,000 live births.

Incidence

Choriocarcinoma is stated by Min Chiu Li[1] to occur once in 30,000 to 50,000 pregnancies among Occidentals and more frequently among Orientals. These figures include abortions, still births, and ectopic pregnancies, and are thus not entirely comparable to our figures, since ours are related to live births only. Chan et al.,[2] reporting on 41 cases over an 8½-year period at Hong Kong University, found one choriocarcinoma per 1,331 deliveries. This relatively high number was misleading, however, since patients with choriocarcinoma were referred to the University Unit for treatment from a larger area than that from which the obstetrical cases originated. If he included only cases in the area during the one year (1961), there were 116,054 total pregnancies, including abortions and ectopic pregnancies, and 19 chorioepitheliomas, giving an incidence of one in 5,882 deliveries or one in 6,250 pregnancies — still a much higher incidence than reported other places. The comparison with our figures again is not entirely possible, since not all of his cases were fatal. Novak and Novak[3] report death rates according to several authors at about 70 to 80% in choriocarcinoma, but in recent years this percentage has undoubtedly decreased somewhat. In general, the incidence of choriocarcinoma and hydatidiform mole in Asia is much higher than in the United States.[4] Hospital figures from reliable clinics in Asia place the incidence of hydatidiform mole at one in 200 to 250 deliveries; similarly, reports of choriocarcinoma range from one in 250 deliveries to one in 3,708. Autopsied cases of choriocarcinoma in three of the largest Asian general hospitals average one in 131 autopsies. Nowhere in the United States is there an autopsy incidence approximating this.

The deaths in the past 12 years from choriocarcinoma in the State of Minnesota occurred during the years as indicated in Table 1. For comparison they are listed with the number of live births for each year.

Age

The mean age at the time of death in the 14 cases of choriocarcinoma in this series was 28. Actually the median age (25) and the mode age (21) are more accurate measures of age distribution, since the curve was markedly skewed. One half of the patients were under 24 years of age, and 10 of the 14 (71%) were 28 years of age or less. Burris[5] pointed out that trophoblastic growths had their highest incidence at the beginning and end of the child-bearing period, a statement which seems to be confirmed by our findings as indicated in Table 2.

The average age of Asian patients was somewhat higher.[4] Chan[2] reports it as 32.1 years.

Parity

Scott,[6] in a review of 175 cases from the Albert Mathieu Registry of chorioepithelioma, points out the increased risk of choriocarcinoma in older age groups, but also the disproportional frequency with which choriocarcinoma occurs with the first pregnancy (Table 3). This finding is also consistent with the maternal mortality series. Half of these cases (seven) had had no previous pregnancies.

In this series there were seven primigravidas: two patients who had had one

Continued

previous delivery and one patient with two previous deliveries. Three patients were listed as gravida 4: one with one living child, one with two living children, and one with three — the other pregnancies being abortions. The 14th patient was a gravida 5 with four living children.

Race and Socioeconomic Status

Thirteen patients were Caucasian and one was Negro, a normal distribution in Minnesota. All were originally private patients, although some were later treated terminally in charity institutions. There did not seem to be any relationship to race or socioeconomic status, as had been suggested by the joint project for the study of choriocarcinoma and hydatidiform mole in Asia.[4]

Case Report

The cause of death in nine cases was listed as metastatic choriocarcinoma. Four patients died as a result of massive intraperitoneal hemorrhage; all of these had metastatic disease also.

Case No. 10-7

One patient died with severe bacteremia associated with granulocytopenia secondary to methotrexate toxicity. Death occurred 10 months after passage of a hydatidiform mole, during which time the patient developed increasing evidence of metastatic disease to the lungs, associated with a rising titer of chorionic gonadotropic hormone. At autopsy there was no tumor such as one ordinarily sees with metastatic malignancy. Microscopic study of the tumor in the wall of the uterus showed a completely amorphous mass; not even the outline of the blood vessels could be made out. The ovaries contained luteal cysts bilaterally. The kidney, pancreas, adrenal, liver and spleen showed no cellular damage. The adrenal showed hemorrhage. Study of the lung showed diffuse necrosis with a minimal amount of purulent exudate. The alveoli in the necrotic area were filled with coagulated serum and blood. The upper lobe showed occasional nodules which seemed to be made up entirely of phagocytes distended with a brown or yellow pigment material, some of the yellow having a vivid color. These phagocytes are present also in the interstitial tissues and occasionally within the alveolar lumen. Some of the nodules in the lung were made up entirely of fresh hemorrhage. There were other areas which were necrotic. None of the nodules in the lung showed any residue or ghost outline of tumor tissue. Apparently the malignant process had been entirely wiped out by methotrexate chemotherapy.

Treatment of these cases consisted of surgery plus X-ray therapy and/or chemotherapy (Table 4).

Surgical

Total hysterectomy was performed in only five of 14 cases, and subtotal hysterectomies in an additional three. In two of these eight cases, treated surgically, the adnexa were left on one side. The reason given was to conserve ovarian tissue.

Case No. 6-32

One case was a 36-year-old spinster who had a hysterectomy for myomata uteri associated with abnormal uterine bleeding. She had no prior dilation and curettage. The pathologist's report showed retained products of a conception thought to be an incomplete abortion plus a preinvasive carcinoma of the uterine cervix. She was subsequently treated with a full course of X ray to the pelvis for the preinvasive carcinoma. Seven years later she died of

TABLE 2
Age Distribution

Age	Cases
16-25	8
26-35	3
36-45	2
46-55	1
Total	14

TABLE 3
Parity

Gravida	Cases
1	7
2	2
3	1
4	3
5	1
6	0
Total	14

TABLE 4
Treatment

1. Surgery		8
With X Ray	7	
Alone	1	
2. Chemotherapy		5
With X Ray	2	
Alone	3	
3. None		1
Total		14

metastatic choriocarcinoma. Review of the original surgical pathology slides showed typical choriocarcinoma of the uterus.

Eight patients received varying doses of X-ray therapy to the pelvis and lung fields, and one patient was treated with a cobalt-60 unit. Four patients were treated with Methotrexate (Amethopterin) — all since 1956 (Table 5).

Other medications include two cases receiving nitrogen mustard terminally along with steroids and blood transfusions.

Type of Pregnancy Preceding Choriocarcinoma

The incidence of type of pregnancy preceding the development of choriocarcinoma was determined and compared with the findings of other authors. Four cases (28.6%) followed spontaneous full-term deliveries; five (35.7%) followed spontaneous abortions; four (28.6%) followed expulsion of hydatidiform mole. One case was found to have a choriocarcinoma of the ovary with no evidence of the disease in the uterus. Five years previously the patient had had what she thought was a spontaneous abortion, but her husband would not allow her to see a physician; consequently, this was never documented. There had been no pregnancies in the intervening five years. She died of metastatic disease. Either this was an abnormal ectopic ovarian pregnancy, primary trophoblastic tumor of the ovary, or the primary choriocarcinoma in the uterus had undergone spontaneous regression. The incidence of ovarian pregnancy is quoted as between one in 25,000 to one in 40,000 pregnancies, or 0.7 to 1.07% of ectopic pregnancies. Acosta-Sisson[7] describes two cases of ab initio choriocarcinoma not affecting the uterus. One patient was age 17 with the primary site of the tumor in the ovary; the other was only age seven with the primary site the structures between the leaves of the broad ligament. Both of these patients died. Neither of them had had a preceding pregnancy (Table 6).

Interval Between Pregnancy and Death

The time interval between onset of disease and death varies considerably (Table 7), apparently due to differences in the latent phase of development of this tumor. However, once extension of the tumor has begun, death almost invariably occurs within 10 to 12 months. Treatment with surgery and the newer chemotherapeutic agents may prolong this period somewhat, and in certain cases provide a cure. In the 14 maternal mortality cases studied the mean survival time from previous pregnancy to death was 23.3 months. This does not correctly present the true picture, however, since two cases survived five years and seven years respectively after the pregnancies. These cases markedly skewed the curve; hence the median (10 months) is probably a more accurate indication of average survival.

Nine cases survived less than one year and 12 cases less than two years. Chan,[2] reporting on 41 cases, showed that the time interval between diagnosis of choriocarcinoma and last pregnancy varied from two weeks to four years. He points out that vaginal bleeding, continuous or irregular, was the prom-

Continued

TABLE 5
Summary of Cases Treated with Methotrexate

Case No.	Dose	Duration of RX	CGH Test		Chest X Ray		Results
			Before	After	Before	After	
8-53	125 mg.	5 days	50,000 m.u.	800 m.u.	+ Vaginal Metast.	+ Metast. to Iliac Crest	Died 20 days after completion of 1st course. 2nd course planned — Patient too sick
10-7	350 mg.	26 days	1:100 dilution	Neg.	+	No Tumor Found	Died five days after last dose (granulocytopenia with sepsis-Pseudomonas)
10-30	50 mg. (then started on Nitrogen Mustard)	2 days	CGH 263,190 i.u.	Not done	+	Not done	Died one day
11-21	750 mg.	340 days	1:100 dilution	+	+	+	Died 23 days after last dose

inent symptom. The uterus was enlarged in more than two thirds of his cases, and male frog tests were positive in 37 of 41 cases. Pulmonary secondaries by chest X ray were found in 29 cases.

One case (7-32) in the 14 classified as choriocarcinoma was actually a malignant mole or chorioadenoma destruens histologically. This patient was a 22-year-old primigravida who passed a hydatidiform mole on September 24, 1954. This was completed with a dilation and curettage. Three months later, December 22, 1954, a second dilation and curettage produced degenerative decidual tissue, and the third dilation and curettage on April 23, 1955, no tissue at all. Chorionic gonadotropic hormone titers were intermittently positive and then negative. At the time of the third dilation and curettage the uterus was noted to be displaced to the left side by a mass 5 x 6 cm. in diameter to the right of the uterus and below the cervix. Pelvic laparotomy was carried out on April 27, 1955. The mass was found to involve the ureter on the right. Dissection of this produced profuse bleeding and shock; thus surgery was limited to a subtotal hysterectomy and partial excision of the mass, followed by packing of the area for hemostasis. Microscopic examination of the tissue showed hydropic placental villi surrounded by trophoblastic tissue. A diagnosis of malignant hydatidiform mole with invasion of the uterine wall and extension into the adjacent soft tissue was made. This was followed up with deep X-ray therapy to the pelvis, and subsequently a right nephrectomy. A second pelvic laparotomy on February 28, 1956, revealed a negative pelvis with no evidence of remaining malignant disease. In spite of this, her Friedman pregnancy tests remained positive and she developed new areas of densities in the lungs and chest, finally succumbing with metastatic disease on August 6, 1956, some 23 months after passing the mole. Autopsy was refused, but evidence of the previous surgical specimen was felt sufficient to make the diagnosis of chorioadenoma destruens.

TABLE 7
Time Interval Between Pregnancy and Death

Time	Cases
Less than 6 months	4
7-12 months	5
13-18 months	1
19-24 months	2
More than 24 months	2
	—
Total	14

Acosta-Sisson[9,10] reported on 41 cases of chorioadenoma destruens in 1960, all but one originating from hydatidiform mole. Hertig[11] stated in 1956 that all cases of chorioadenoma destruens were preceded by moles. Ten of Acosta-Sisson's cases (24.39%) developed uterine perforation and 11 cases (26.82%) metastasized. The mortality rate was four (9.75%). Wei[12] of Taiwan reports 25% metastasis in 12 cases of chorioadenoma destruens and Prawirhardjo[13] in Indonesia, 50% of 10 cases. Chorioadenoma destruens does not spread as fast nor does it metastasize as frequently to distant areas as choriocarcinoma. However, it certainly can not be considered a benign tumor, as it is endowed with the vitality of growth, metastasizes, and poses a danger to the life of the patient.

Comments

The review of the management of these cases by the Maternal Mortality Committee produces some interesting findings. Only two of 14 cases had what is generally considered adequate prenatal care by the Minnesota State Maternal Welfare and Maternal Mortality Committee standards. In all fairness, it must be pointed out that six patients had no prenatal care, either because they did not present themselves to a physician for care

TABLE 6
Percent Incidence of Type of Pregnancy Preceding
Choriocarcinoma According to Different Authors

						(Acosta-Sisson[8])	
	Novak & Seah USA (74 Cases)	Chan (41 Cases)	Hasegawa Japan (257 Cases)	Prawirohardjo Indonesia (27 Cases)	Wei Taiwan (17 Cases)	Acosta-Sisson Philippines (88 Cases)	Minn. Maternal Mort. Series (14 Cases)
Hydatidiform Mole	39.2%	43%	67.9%	70.4%	35.3%	57.9%	28.6%
Abortion	37.8%	29.3%	25.4%	14.8%	23.5%	22.7%	35.7%
Term Pregnancy	23%	24.4%	6.3%	7.4%	17.6%	11.4%	28.6%
Tubal Pregnancy		2.4%			11.8%		
Concomitant with 5 mos. Pregnancy						1.13%	
Ab Initio Chorio						6.81%	7.1%

or did not know they were pregnant. Two more had their prenatal care out of state and hence could not be evaluated. Of the remaining, four had prenatal care which was considered faulty but noncontributory, consisting of incomplete physical and pelvic examinations or lack of the usual routine laboratory studies.

Management of Labor

The management of labor and delivery was felt to be adequate in only four cases. Again two cases were managed out of state and hence could not be evaluated. In five more cases no judgment could be made regarding management of labor and delivery, since three of these aborted at home and two had no evidence of pregnancy before being treated for their disease. In only two of the remaining three cases was faulty management of labor and delivery felt to be possibly contributory.

1. Case 7-32 was delivered of a hydatidiform mole on September 24, 1954. A sponge forceps was used to wipe off the uterine cavity but curettage was not done until three months later. Failure to carry out uterine curettage shortly after passage of the hydatidiform mole may well have delayed the diagnosis and treatment of the disease, in addition to leaving molar tissue behind. The patient died 23 months later of metastatic chorioadenoma destruens.
2. Case 2-51 aborted in bed in the hospital on June 16, 1951. The tissue was saved by the nurses for examination by the physician; however, he neither examined it nor submitted it to microscopic examination. Two days later curettage was done and again no tissue submitted for pathologic examination. Three months later at laparotomy the diagnosis of choriocarcinoma was made. Again it is difficult to determine whether an earlier diagnosis would have saved this patient, but certainly her prognosis was not enhanced by the delay.

Management of Puerperium

Management of the puerperium and/or care at hospitalization was considered adequate in only four cases. One additional case could be considered adequate, except that there was a delay in diagnosis due to prolonged chiropractic treatments before the patient returned to her physician. The remaining cases had faulty management, but not all were considered contributory. In four of these the faulty management was assigned to the pathologist because of an incorrect diagnosis of tissue submitted.

1. Case 1-68. Here a delay in diagnosis was attributed to the pathologist who interpreted the curettings from a dilation and curettage on June 12, 1950 as an incomplete abortion. Three months later review of the slides by the pathologist showed typical choriocarcinoma.

2. Case 6-32. A 46-year-old female had had a total hysterectomy in 1949 for abnormal uterine bleeding. Six years later she died of metastatic choriocarcinoma. The review of the slides from her original surgery revealed typical choriocarcinoma.

3. Case 6-37. A dilation and curettage on June 6, 1955, two months postpartum was interpreted as retained placental tissue. Review of the slides, although not diagnostic of carcinoma, showed enough suspicious areas to suggest a repeat dilation and curettage. This suggestion was not made, however, and probably contributed to delay in the diagnosis and treatment of this patient. A second dilation and curettage three months later, September 6, 1955, showed obvious choriocarcinoma.

4. Case 8-53. A dilation and curettage on December 3, 1957, three weeks postpartum, demonstrated obvious choriocarcinoma. However, the pathologist was unsure of the diagnosis and delayed a final diagnosis for two weeks, while obtaining other opinions. This, however, probably did not influence the final outcome.

The five remaining cases had faulty care during the puerperium, attributable to the attending physician; but in only one could faulty care be considered contributory.

Case 10-7. The patient passed a hydatidiform mole on August 26, 1958. Dilation and curettage was diagnosed as benign by the pathologist. However, the patient continued to show positive pregnancy tests even with dilute specimens. Repeat dilation and curettage was delayed five months (until January 8, 1959) and still showed no evidence of trophoblastic tumor. Again treatment was delayed until May 19, 1959, when methotrexate therapy was started because the patient had obvious metastatic disease with elevated chorionic gonadotropic hormone titers. She then received an excessive dose of methotrexate (350 mg. over a 26-day period) and died of methotrexate toxicity. It was felt by the committee that earlier and qualified consultation might have altered the patient's course.

Two cases were considered to have faulty management by the attending physician because of incomplete surgery, but this was not considered contributory to the outcome. One patient had obvious vaginal metastases, but these were not recognized as such by the attending physician. The diagnosis could have been confirmed earlier if these had been biopsied, but this probably would not have altered the outcome. Finally one patient had

Continued

a delay of three months with abnormal uterine bleeding before dilation and curettage and before a diagnosis of choriocarcinoma was established.

Hertz,[14] reporting on 65 patients treated over the past five years with the folic acid antagonist amethopterin (methotrexate) or Vincoleukoblastin, an oncolytic alkyloid derived from Vinca Rosea, points out that the most critical factor in survival of the patient is the duration of the disease before chemotherapy is started. Of 25 patients treated within four months of the onset of the disease, 18 had complete remission, whereas only seven of 27 treated later than six months after onset showed such a favorable outcome.

A review such as this brings to light the errors in management, the delays and omissions which enhance or contribute to the demise of a patient. In most instances these seem to be errors of omission, perhaps due to lack of a "high index of suspicion." The rarity of the lesion certainly plays an important role in the tendency to overlook this disease as a possible cause of the patient's symptoms. In only one instance could the patient's poor outcome be attributed to an error of commission and this was undoubtedly due to unfamiliarity with the toxicity of a new chemotherapeutic agent (methotrexate).

Conclusion

Deaths from choriocarcinoma in Minnesota are extremely rare: one per 70,000 live births, a considerably lower incidence than that reported in Asia, Southeast Asia, Japan, Taiwan, and the Philippines. Whether the etiology is due to racial differences, differences in socioeconomic or environmental situation, genetic inheritance, or differences in maternal antibody response to the embryonic tissue is yet undetermined. The answer to this may well have to come from the areas where the incidence is of such a nature that sufficient material is available for study.

There seems, also, to be a difference in average age of the patient with choriocarcinoma in Minnesota as compared to the Southeastern Asian countries. Over 70% of our cases were 28 years of age or less, and half were under 24. The median age was 25.

Socioeconomic status did not seem to play a part in the development of choriocarcinoma in the series. All patients were private patients and all but one, Caucasian.

The cause of death in most instances (nine cases) was metastatic disease; however, four patients died of interperitoneal hemorrhage and one of methotrexate toxicity.

Treatment consisted primarily of surgery plus X-ray therapy, although only eight of 14 patients had a hysterectomy, three of these subtotal. Since 1956, most cases have had some chemotherapy (methotrexate), the dosage ranging from 50 mg. over two days (terminal) to 750 mg. over 340 days.

The incidence of type of pregnancy preceding development of choriocarcinoma was term pregnancy (28.6%), abortion (35.7%), hydatidiform mole (28.6%), with one case thought to represent an ab initio choriocarcinoma of the ovary. The percent of cases following term delivery is higher than most cases reported in the literature. This may not be significant, since the series (14 cases) is small. On the other hand these cases are all deaths from trophoblastic tumors and may indicate a poorer prognosis for those patients who develop choriocarcinoma associated with a term pregnancy.

Nine (64%) of 14 cases died of their disease in less than one year after its onset; twelve (86%) were dead within 24 months. These findings are in keeping with other published reports.

The review of the management of these cases reveals many areas of faulty diagnosis and treatment. Some errors in the management could not be considered contributory to the outcome for the patient, but the delays in diagnosis and treatment in many cases, particularly now that a chemotherapeutic agent is available for their care, seem to be definitely contributory to the patient's demise. Most of the errors are errors of omission and thought to be due to oversight on the part of the attending physician and/or pathologist because of the rarity of the disease. A plea is made for a higher index of suspicion in all cases of abnormal bleeding, particularly in the postpartum period following abortions and the passage of hydatidiform moles. Prompt and thorough investigation would be rewarded with earlier diagnosis and presumably a better prognosis from earlier treatment.

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To cure lumbago, if the pain is in the right foot, reduce to powder with your right hand the wings of a swallow, then make an incision in the swallow's leg and draw off all its blood. Skin it and roast it and eat it entire. Then anoint yourself with the oil for three days and you will marvel at the results.

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*Thorndike, Lynn: See Minn Med Oct. '63.

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Perinatal Mortality Study

Diaphragmatic Hernia — Congenital

The following case illustrates one of the most frequent congenital defects responsible for death in the newborn period which is a salvagable situation.

This male infant was delivered at a Minneapolis hospital. This was the second pregnancy of a twenty-year-old mother, her only previous pregnancy having ended in a spontaneous early abortion. The baby's delivery was spontaneous and uneventful. The birth weight was 7 lbs. 8½ oz.

The condition of the baby was poor at birth. There was poor muscle tone, and he was cyanotic. Respirations were shallow, labored and grunting. The pulse rate was 110. There was no cough or swallowing reflex. An endotracheal tube was inserted and oxygen given with positive pressure. Auscultation of the chest revealed the presence of rales within the right lung with markedly decreased breath sounds over the entire left chest. There were occasional gasping respirations, not improved with coramine. The infant expired at 5:20 P.M. on the day of birth, that is, he did survive for 77 minutes. Autopsy revealed:

1. Congenital diaphragmatic hernia, Left
2. Pulmonary atelectasis and hypoplasia secondary to #1
3. Mediastinal shift secondary to #1

Comments

In an infant with obvious respiratory distress in the newborn period, a portable chest film should be taken if possible at the earliest possible moment.

If diaphragmatic hernia is suspected in a newborn baby who is obviously terminal, no harm could be done by a small abdominal incision for removal of the viscera from the chest. If the diaphragmatic hernia is present, this can be life saving, especially with an anesthesiologist already in attendance and an endotracheal tube in place. If diaphragmatic hernia is strongly suspected and the baby is in a terminal state, obviously no harm would be done even if a hernia was not found.

If the chest film has been made and a diaphragmatic hernia is definitely present, at any time that the child becomes severely cyanotic, there is no question but what an abdominal incision should be made for removal of the viscera from the chest, even if operating room and sterile instruments are not available.

The creed of the true saint is to make the best of life, and make the most of it.
—Chapin

The best way to make children good is to make them happy.—Wilde

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Meetings And Announcements

APRIL

Eighth postgraduate course on fractures and other trauma sponsored by the Chicago Committee on Trauma of the America College of Surgeons, April 22-25, John B. Murphy Memorial Auditorium, Chicago. Contact: Committee, 1791 W. Howard Street; Chicago.

University of Colorado Medical Center postgraduate course "Clinical Dermatology" April 23-25, Denver, Colorado. Contact: The University in Denver.

MAY

Minnesota State Medical Association 111th Annual Meeting, Mayo Civic Auditorium; Rochester, Minnesota, May 18-19-20. Contact: Harold Brunn, 496 Lowry Medical Arts Bldg.. St. Paul.

American Rhinologic Society Samuel Iglauer Memorial Lectures, University of Cincinnati College of Medicine, May 9. Contact: American Rhinologic Society; 530 Hawthorne Place; Chicago.

American Society of X-Ray Technicians Convention, Leamington Hotel in Minneapolis, May 30-June 5. Contact: Sister Mercedes, St. Joseph's Hospital, St. Paul.

Aerospace Medical Meeting, May 11-14, Americana Hotel, Bal Harbour, Miami, Florida. Contact: Wm. Kennard, M.D., Aerospace Medical Association, Washington National Airport, Washington, D. C.

Chicago Ophthalmological Society Meeting, May 22-23, Drake Hotel, Chicago. Contact: Arlyne Schulz, 5552 N. Olcott, Chicago.

American College of Physicians postgraduate course, May 11-15, Georgetown University Hospital, Washington, D. C. "Clinical Auscultation of the Heart." Contact: Edward Rosenow at the College in Philadelphia.

American Proctologic Society Meeting, May 9-14, Bellevue Stratford Hotel; Philadelphia, Pa. Contact: Harry E. Bacon, M.D., 255 South 17th St., Philadelphia.

JUNE

Minnesota State Medical Assistants Society Meeting, June 5-7, Radisson Hotel, Minneapolis. Contact: Marjorie Johnson, 3428 Pleasant Avenue South, Minneapolis, Minnesota.

ANNOUNCEMENTS

Applications for certification in the American Board of Obstetrics and Gynecology now being accepted. All applications must be submitted by July 1, 1964. Contact: Robert Faulkner, M.D.; 2105 Adelbert Road; Cleveland, Ohio.

* * *

University of Minnesota Continuation Medical Courses.

May 4-6	Ophthalmology
May 14-16	Surgery
May 27-29	Otolaryngology

* * *

The next scheduled examination (Part II), oral and clinical, by the American Obstet. & Gyn. Board will be conducted for all candidates at the Edgewater Beach Hotel, Chicago, Illinois by the entire Board, April 27-May 2. Candidates will be sent notice of examination dates.

To be seventy years young is sometimes far more cheerful than to be forty years old.—Don Herold

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It is one of the most detestable habits of a Lilliputian mind to credit other people with its own malignant pettiness.—Balzac - Pere Goriot

The discharged
mental patient . . .
and Thorazine®
brand of chlorpromazine

"The average practitioner is quite capable of handling the vast majority of ex-institutionalized patients by regulation of medication, reassurance, manipulation of the environment where necessary, and . . . other technics." Kline, N.S.: Postgrad. Med. 27:620 (May) 1960.

The family physician must often assume responsibility for the discharged mental patient. Thorazine (chlorpromazine, SK&F) can be a valuable adjunct to the continuing care of this patient, because it helps prevent relapses by insulating him from the impact of stressful experiences. For successful rehabilitation and prevention of rehospitalization, however, the former mental patient—and often his family—also needs the guidance and counsel of his physician.

Many physicians are surprised by the high doses of Thorazine (chlorpromazine, SK&F) used in patients released to their care from mental hospitals. This surprise may be expressed by a drastic reduction in dosage "to play it safe"—with serious consequences for the patient.

The successful maintenance of former mental patients requires adequate, often "high" dosage, and often for prolonged periods of time. Fortunately, these dosages do not mean greater risks for the patient. On the contrary, there is much less risk of serious side effects once a patient has become gradually accustomed to Thorazine (chlorpromazine, SK&F)—*regardless of dosage*—over a period of a few months. Continuing therapy is almost always well tolerated, and is essential to most patients' continued well-being.

Brief Summary: Thorazine (chlorpromazine, SK&F) has been successfully used for 10 years in the treatment of mental and emotional disturbances, and has proven highly effective in the maintenance therapy of former hospitalized mental patients. *Principal side effects:* The most frequently encountered side effect is transitory drowsiness. Other occasional side effects include: dry mouth, nasal congestion, constipation, miosis, dermatological reactions, photosensitivity, jaundice, hypotension, increased appetite and weight; very rarely, mydriasis, agranulocytosis, extrapyramidal symptoms. *Contraindications:* Comatose states or in the presence of excessive amounts of C.N.S. depressants.

For complete prescribing information, please see *PDR* or available literature.

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WHERE MINNESOTA DOCTORS WILL BE IN '64

Mayo Centennial Highlights — 111th Annual Meeting Program

The 111th Annual Meeting of the Minnesota State Medical Association will be held May 18, 19, and 20 in Rochester in the atmosphere of the Mayo Centennial observance. In 1964 the Mayo Clinic will observe its centennial year; the Mayo Foundation its fiftieth year; and the University of Minnesota its seventy-fifth year. These events will contribute immeasurably to the "once in a hundred year's opportunity" for physicians to join in paying tribute to a century of medical achievement.

The House of Delegates will convene Sunday, May 17, at 2 p.m. and Tuesday, May 19, at 9 a.m.

"The Status of Immunization — 1964" is the title of the paper scheduled for presentation by Dr. Harold G. Muchmore, St. Paul, at the opening of the scientific session Monday, May 18, at 10:00 a.m. A varied program of lectures, demonstrations, round table luncheons, committee breakfasts and fireside discussions has been arranged by the committee on scientific assembly for the two and one half days.

A number of outstanding speakers, locally and nationally renowned, will appear on the scientific program. Scientific program participants will include: Doctor Robert Turell, New York; Doctor Lenox Baker, Duke University Medical Center, Durham, North Carolina; Doctor Thomas E. Starzl, Chief Surgical Service, Denver 20, Colorado; Doctor Belding Scribner, University of Washington, Department of Medicine, Seattle, Washington; Doctor Chauncey D. Leake, University of California, San Francisco Medical Center; Doctor Francis O. Kelsey, Chief Investigational Drug Branch, Washington D. C. and others.

"A Centennial Tribute" to the Mayo Clinic and Foundation will be given at the annual banquet Tuesday, May 19, by Dr. Lloyd G. Stevenson, Professor, Department of Science and Medicine, Yale University. At the banquet, the Fifty Club candidates will be the honored guests and a medal for the outstanding scientific exhibit will be presented by the Southern Minnesota Medical Association. Outstanding entertainment featuring a floor-show and dancing will follow the banquet program.

The American Medical Association president, Dr. Edward R. Annis, will be the speaker at the New Members, County Officers and Delegates banquet, Sunday night, May 17.

Dr. Charles W. Mayo will be the guest speaker at the Annual Spring Banquet of the Minnesota Academy of General Practice, Monday, May 18, at the Kahler Hotel. "The elder citizen — whose responsibility?" is the title of Dr. Mayo's address.

A series of six Fireside Conferences have been scheduled for Monday, May 18, beginning at 9:00 p.m. The Fireside Conferences are sponsored by the Minnesota Chapter of the American College of Chest Physicians and the Minnesota State Medical Association.

The following will be the topics for the tables planned for the Conferences: Congestive Cardiac Failure; The Present Role of Surgery in Heart Disease: Asthmatic Bronchitis and Emphysema; Bronchogenic Carcinoma — Etiology, Recognition and Management; Acute Pneumonia; The Clinical Syndromes and Management of Ischemic Cardiac Disease.

The second duplicate bridge tournament to be held in conjunction with the annual meeting has been scheduled for Monday, May 18, at 9 p.m. The tournament is open to all players. Duplicate experience is not necessary. This will be a non-master point game. Trophies will be given for first and second place winners.

A number of the special events and social activities require advance registration. Physicians wishing to attend these events are requested to make arrangements in advance as requested.

Many of the scientific and non-scientific committees have planned breakfast meetings in conjunction with our meeting. Kindly check the official annual meeting program for the date, time and place for your committee meeting.

Members of the Minnesota Academy of General Practice are hereby informed that attendance at the Tuesday, May 19, scientific programs is approved for five accredited hours by the American Academy of General Practice. This popular annual feature is sponsored jointly by the Minnesota Academy of General Practice and the Minnesota State Medical Association.

Scientific Program

Mayo Civic Auditorium

MONDAY, MAY 18, 1964

A.M. Visit scientific and technical exhibits
10:00 STATUS OF IMMUNIZATION—1964
Harold G. Muchmore, St. Paul
10:30 TRANSPLANTS
Thomas E. Starzl, Denver
HEMODIALYSIS IN THE TREATMENT OF CHRONIC UREMIA
Belding H. Scribner, Seattle
11:30 MORAL AND LEGAL ASPECTS OF TRANSPLANTS AND DIALYSIS
Chauncey Leake, Ph.D., San Francisco, California
12:15 ROUND TABLE LUNCHEONS
1:30 Visit scientific and technical exhibits
2:10 PROBLEMS CONCERNING THE STUDY AND TREATMENT OF STROKES
Clark H. Millikan, Rochester—moderator
H. L. Baker, Jr., Rochester
Robert G. Siekert, Rochester
J. P. Whisnant, Rochester
C. S. MacCarty, Rochester
3:15 Visit scientific and technical exhibits
4:00 CHRONIC PULMONARY DISEASE
Management in Children
Norman A. Sterrie, Minneapolis
Drug and Inhalation Therapy
James P. Lillehei, Minneapolis
9:00 Fireside Conferences

TUESDAY, MAY 19, 1964

This program is acceptable for five accredited hours by the American Academy of General Practice

A.M. Visit scientific and technical exhibits
9:00 DISEASES OF THE COLON
Robert Turell, New York City
9:30 DIAGNOSIS OF CONGENITAL HEART DISEASE
Lewis S. Carey, St. Paul
William F. Mazzitello, St. Paul
10:15 Visit scientific and technical exhibits
11:00 EMERGENCY CARE OF TRAUMA . . .
ON THE FACE
Conrad I. Karleen, Minneapolis
IN THE CHEST
N. K. Jensen, Minneapolis
IN THE ABDOMEN
John F. Perry, Jr., St. Paul
12:15 ROUND TABLE LUNCHEONS
1:30 Visit scientific and technical exhibits
2:10 VASCULAR INJURIES IN FRACTURES
Lenox D. Baker, Durham, North Carolina
2:30 CARE AND FEEDING OF PREMATURE INFANTS
James N. Berbos, Aberdeen, South Dakota
3:15 Visit scientific and technical exhibits
4:00 RADIATION IN PREGNANCY
Karl K. Latteier, Detroit, Michigan
4:30 DRUGS IN PREGNANCY
Frances O. Kelsey, Washington, D. C.
7:00 BANQUET
Presentations
CENTENNIAL TRIBUTE
Lloyd G. Stevenson, Professor, History of Science and Medicine, Yale University
RESPONSE
J. Minott Stickney, Rochester
Entertainment, Dancing and Late Evening Buffet

OBSTETRIC MANIKIN DEMONSTRATION
Fred A. Lyon, University of Minnesota Medical School
Times: 10:15 A.M.
1:30 P.M.
3:15 P.M.
5:00 P.M.
Place: Demonstration Room, Auditorium

WEDNESDAY, MAY 20, 1964

A.M. Visit scientific and technical exhibits.
9:00 CUTANEOUS MANIFESTATIONS OF GASTROINTESTINAL DISEASE
Harold O. Perry, Rochester—Moderator
Lloyd G. Bartholomew, Rochester
James C. Cain, Rochester
Walter R. Nickel, San Diego, California
9:45 RECENT ADVANCES IN HEARING SURGERY
O. E. Hallberg, Rochester
10:15 Visit scientific and technical exhibits
11:00 UROLOGY IN CHILDREN
Arnold S. Anderson, Minneapolis—Moderator
T. H. Sweetser, Jr., Minneapolis
David C. Utz, Rochester

ROUND TABLE LUNCHEONS

KAHLER HOTEL

MONDAY—12:15 P.M.

Immunization in Children
Harold G. Muchmore, St. Paul
Problems of Transplants
Thomas E. Starzl, Denver, Colorado
Salt and Water Needs of Patients
Belding H. Scribner, Seattle, Washington
Who will Educate the General Practitioner?
James C. Cain, Rochester — NIH
Davitt A. Felder, St. Paul — NAME
Future Possibilities in Transplantation of Kidneys
Chauncey D. Leake, Ph.D., San Francisco, Calif.; William D. Kelly, Minneapolis
Practical Considerations in the Diagnosis of Dizziness
Clark H. Millikan, Rochester

TUESDAY—12:15 P.M.

Hemorrhoids and/or Anogenital Pruritus
Robert Turell, New York, New York
Athletes and the Treatment of Their Injuries
Lenox D. Baker, Durham, North Carolina
The New Drug Laws in Action
Frances O. Kelsey, Washington, D. C.
Postpartum Complications
James N. Berbos, Aberdeen, South Dakota
Practical Considerations in Treatment of Eczemas of the Hands
Walter R. Nickel, San Diego, Calif.
Vascular Radiology in General Practice
Lewis S. Carey, St. Paul

Sports Events

SUNDAY, MAY 17, 1964

GENERAL INFORMATION: Participants in sports events, their wives, and all who attend the Annual Meeting are invited to attend a Sports Events Buffet at 5:00 P.M. at the Rochester Golf and Country Club. Tickets for the buffet, $4.00, gratuity included.

GOLF TOURNAMENT

Place: Rochester Golf and Country Club
Tee-off Time: 10:00 A.M.–12:00 Noon—Sunday
Prizes will be awarded to the low scorers. Green fees $7.00.

SKEET AND TRAP EVENTS

PLACE: Rochester Gun Club—The Club is located ¼ mile west of St. Mary's Hospital on old Highway 14 behind the golf driving range on the north side of the highway.
Time: 1:00 P.M.–4:00 P.M.—Sunday. Events will include regular skeet and trap rounds of 25 shots in each round. Prizes will be awarded at the Sports Events Buffet at the Rochester Golf and Country Club.

Presidents Letter continued from Page 363

price and quality cutting, leaving its sponsors, the medical profession, without recourse to a quality prepayment plan controlled by medical men. Those who feel the impact, economically and politically, are not primarily the patients or the planners but our own profession.

Philosophically, this period of twenty years has seen the introduction of a new category of trade or employment. These persons and groups wish to assume the function of socioeconomic planning and control of medical practice. They claim credit for a multitude of good works but disclaim a multitude of sins. The Biblical saying that charity covers a multitude of sins hardly applies here because charity seems to have eluded these self-appointed sponsors of medical care. True medical associates, the paramedics who are technicians and others medically and technically trained, are welcomed; but the fringes contain economists, public relations experts, sociologists, promoters, etc., etc. These are the persons whose principal purpose is opportunity for themselves. They lack preparation and understanding but have a tremendous desire for power in the medical field without knowledge of a physician's motivation. Their ascendancy has taken advantage of the busy doctor and relegated him to the background. What, then, has happened? Today, 1964, sees our profession attacked by the onslaught of nonmedically trained persons who dictate medical programs, who are uninterested in the patient, but who are on a campaign for power and profit.

It is my hope, as President of this Association and as a member of Blue Shield, that the 1964 meetings of the Minnesota State Medical Association and Blue Shield Corporation will take positive action to again place prepayment plans and their guidance in the hands of the profession so as to renew quality in the best interests of the public. We should pledge ourselves to guide Blue Shield and others who wish to provide real coverage by giving counsel and aid. We should support our own plan by bringing its direction into the hands of 1964 doctors. We should rebuild its programs and recognize the present status of the patient, which includes his health and his family's health, and which encompasses the employer and the employee on a sound medical-economic basis.

We must not rest or stand idle; in the interest of our patients and our freedom of practice, we must not be just up-to-date but far-seeing. Let us as a profession provide leadership by recovering control of our plan.

J. P. Medelman M.D.

J. P. Medelman, M.D.
President
Minnesota State Medical Association

Medical Economics

Health Insurance Protection High in Minnesota

The people of Minnesota have reached a high level in health insurance protection, reports the Health Insurance Institute. As of December 31, 1962, 80 per cent of the state's population were covered by some form of health insurance for the costs of hospital and medical care. This compares with the national figures of 76 per cent of the civilian population — some 141 million persons — having health insurance.

The following fact sheet incorporates the latest available data — drawn from hospital, medical, insurance and government sources — on health insurance and health care for Minnesota.

Extent of Health Insurance Coverage and Other Figures

—Number of persons with hospital expense insurance	2,784,000*
—Number of persons with surgical expense insurance	2,513,000*
—Number of persons with regular medical expense insurance	1,812,000*
—Number of persons with major medical insurance	752,000*
—Total health insurance benefits paid (1961)	$132,917,000
By insurance companies for hospital, surgical and medical care, including loss of income	$79,025,000
By Blue Cross-Blue Shield and other plans for hospital, medical and surgical care	$53,892,000
—Number of health insuring organizations licensed in the State	283
(263 insurance companies, 2 Blue Cross-Blue Shield and similar groups, and 18 other health plans)	

Hospital Statistics

—Number of hospitals** in state (1962)	176
—Number of hospital beds available (1962)	17,472
—Number of persons admitted during the year (1962)	568,100
—Number of persons under hospital confinement on an average day	12,440
—Average length of time patient remained in hospital	8 days
—Average cost per hospital stay	$294.67

Professional Services

—Number of practicing physicians (1962)	2,981
—Number of practicing dentists (1962)	2,470
—Number of registered pharmacists (1962)	2,329

---

*Net total of people protected — eliminates duplication among persons protected by more than one kind of insuring organization or more than one insurance company policy providing the same type of coverage.

**Nonfederal, short-term general and other hospitals.

Minnesotans Carry 9th Highest Load of State, Local Taxes

A current statistical report issued by the United States government "offers justification to Minnesotans who are 'griping' about high state and local taxes," Charles P. Stone, General Counsel of the Minnesota Taxpayers Association, said recently.

"In fiscal 1962 the load of state and local taxes in Minnesota averaged $250.51 for each of the State's 3,461,000 men, women and children," Stone said, citing figures from a Bureau of the Census report titled "Governmental Finances in 1962" (October, 1963). "This was $27.05 or 12.1% above the national average.

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"At the same time, Minnesotans had a lower-than-average ability to pay these taxes. Their personal income during this same period averaged $2,236 per capita, which was $130 or 5.5% below the national average.

"On a per-person basis, only eight of the 50 states placed a higher load of state and local taxes on their people: New York, California, Nevada, Massachusetts, Connecticut, Colorado, Washington and Hawaii. But in each of these states the ability to pay, as reflected by average personal income, was higher than in Minnesota. In New York, for example, where the average tax load was $58.54 more than in Minnesota, the personal income average was $694 above ours.

"Had Minnesota's personal income level been up to the national average in 1962, and its level of state and local taxes been down to the national average, the average citizen would have had an additional $157.05 to spend or save.

"This might not seem like much, on a per-person basis, but over-all it would have given a $543,500,000 boost to Minnesota's general economy."

National Independent Business Group Opposes Medicare

"The expected forthcoming renewal of the debate on Medicare financed by increased Social Security taxes should be conducted on a high plane of honesty, without seeking to delude the public with a 'numbers game' ", C. Wilson Harder, president of the National Federation of Independent Business, which has long been opposed to the proposed legislation, said recently. The public should know, he said, that a 15.8% tax increase is proposed. The National Federation of Independent Business, Inc. is the largest individual membership of any business organization in the United States. It claims a national membership of more than 190,000 independent business proprietors.

Mr. Harder pointed out that proponents of the plan emphasize that the program of giving free medical care to everyone reaching the age of sixty-five, regardless of their need, emphasize heavily that it would only require a ¼ of 1% increase in the tax deducted from the worker's paycheck and a like increase in employer contribution.

Medicare Would Nulify Tax Cut

Largely minimized is the fact that tied in with this ½ of 1% increase is a broadening of the base from the present tax on the first $4,800 of earnings per year to $5,200 per year. This will result in both employer and employee paying 15.8% more Social Security taxes.

Based on the reported 1963 Social Security tax collections totalling $21,900,000,000, this increase would result in $3,460,200,000 more taxes being collected. Of this increase slightly more than half would come from the employers, while the employees would have about $1,500,000,000 less take home pay.

"In effect," Mr. Harder pointed out, "this one proposal would wipe out immediately over 25% of the gain to the economy achieved by the current income tax reduction approved by the Congress."

Independent Business Opposes Medicare

In the nationwide voting conducted in 1963 by the Federation among the nation's independent business proprietors, 83% voted opposition to Medicare. In a vote taken the previous year, the opposition was only 77% and in the vote taken on the same issue a year before that, the opposition was 73%.

"Somehow," Mr. Harder commented, "the businessmen do not see why they should be burdened with more taxes, and why their employees should be deprived of more of their earnings so that well-to-do and wealthy people should get free medical care just because they have reached their sixty-fifth birthday."

He also pointed out that there is no certainty that the tax could remain at that level, and that the proposed $3.5 billion tax increase to start with could rapidly balloon to several times that amount.

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References: (1) Moyer, J. H., and Heider, C.: Am. J. Cardiol. 9:920 (June) 1962. (2) Brest, A. N., and Moyer, J. H.: Pennsylvania M. J. *63*:545 (Apr.) 1960. (3) Berry, R. L., and Bray, H. P.: J. Am. Geriatrics Soc. *10*:516 (June) 1962. (4) Hutchison, J. C.: Current Therap. Res. *4*:610 (Dec.) 1962. (5) Feldman, L. H.: North Carolina M. J.: *23*:248 (June) 1962.

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Bibliographical references should be limited to twelve and should be typed in conformity to the method used by the Index Medicus. They should be numbered consecutively in the order in which they first appear in the text. Book references should give the name of the author, title, edition number, publisher, and the year.

Illustrations (photographs, tables, and graphs) should be submitted on separate sheets of paper and not combined in the text. Instructions for combining photographs are acceptable.

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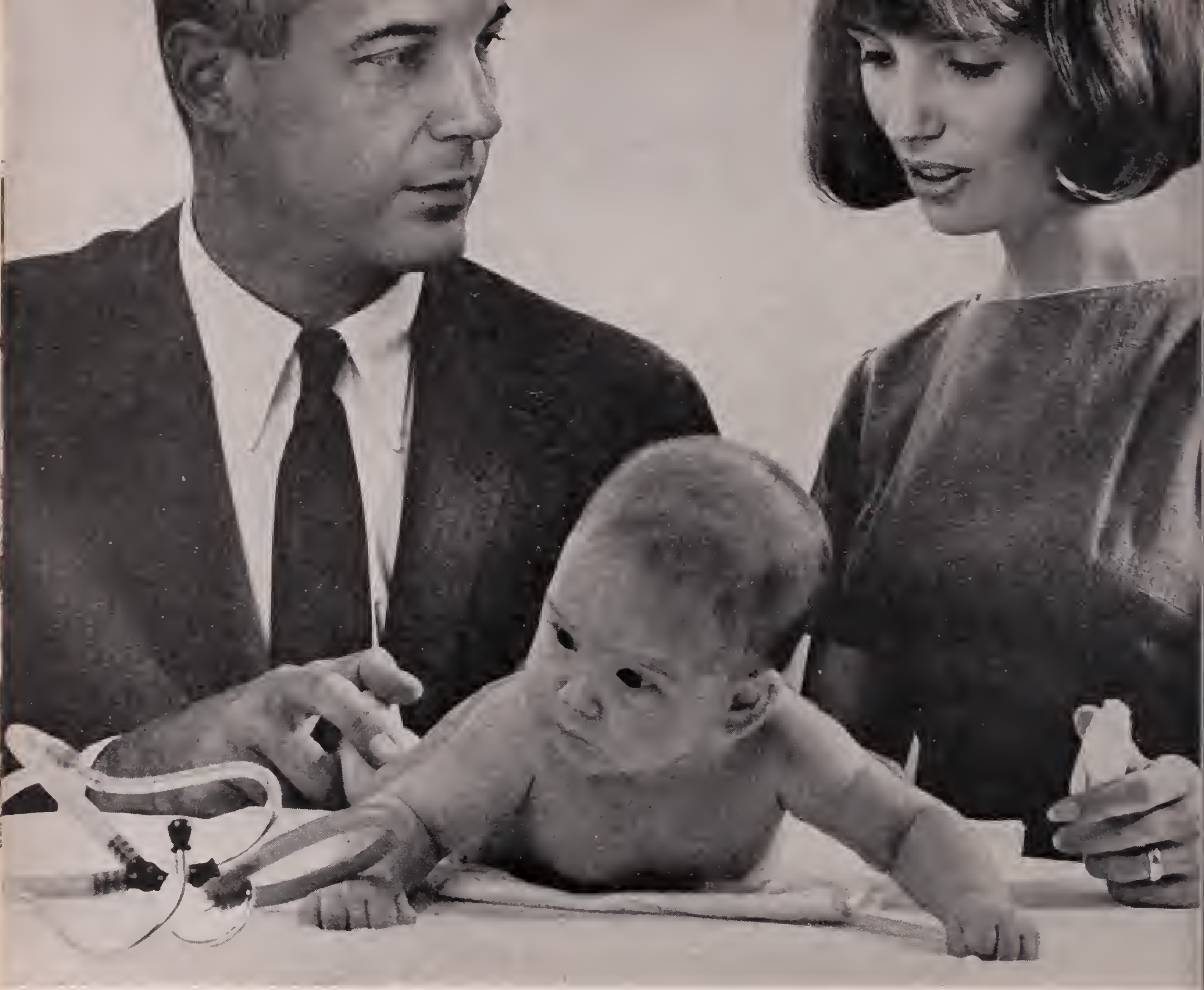

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*Donnelly, J.: A.M.A. Arch. Environmental Health 6:697, June, 1963

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President's Letter

Being now almost at the half-way mark in writing this "President's Letter" on a monthly basis, I am wondering whether anyone other than the author, the editors and the proofreaders look at it — or, what is more important, read it. In spite of extensive research I find it impossible to come up with a joke each month that is new to the majority of my potential readers so that avenue of getting attention is out. My small circle of friends, upon being specifically questioned, assure me that they enjoy the fruits of my labors in this effort, having consumed and digested every word, but they seem somewhat less than nourished by that metabolic process because they are unable to recollect the tasty morsels that have been dished out. Perhaps a future president of the Association will revolt and refuse to be a space-filler for this Journal. If so, these observations open the way for him to spend some of his "leisure" time to better advantage on affairs in the grand manner rather than on these monthly cook-outs.

Tradition, however, impels me to serve another course of the same old menu. I choose to try to make palatable a few tid-bits on the topic of Drugs.

As is well known to physicians, the public now regards drugs as a staple item. Americans demand drugs as a necessity and as a right in the same way that they consider packaged and processed foods to signify their privileges and freedom. Food in its natural state is regarded as outmoded and fit only for backward people. Consumption of drugs is considered to be a sign of enlightenment and progress.

We as physicians know that there is no drug that is completely safe. Any chemical agent administered by any route to a person carries with it an element of risk.

There has been appointed a legislative Commission on the Sale of Home Remedies which is conducting hearings on the proper manner by which to regulate the acquisition of medications by the people of Minnesota. Presumably, this commission is concerned only with the problem of protecting the public health and it has no regard for any possible political aspects of the matter. The commission has been instructed to report to the State Legislature at the next regular session. It is undertaking a complex proceeding requiring complete understanding of the present Pharmacy Act, the decision of the Minnesota State Supreme Court on the subject handed down in February of 1962, and the proposals of various interested groups who seek change in the present regulations on the sale of drugs either in the direction of liberalization or stricter control. Every member of our Association should also familiarize himself with the matter because of our knowledge that self-dosing is a dangerous business.

In meetings with the State Board of Pharmacy and the State Pharmaceutical Association (not to be confused with the Association of Retail Druggists), I have been impressed by their sincerity and concern for the protection of the public in regard to drug availability and control.

I have assured our friends of the Pharmacy Board and Association that it is the earnest hope of physicians that they will come up

Continued on Page 552

the vat
that foils
the "leakers"...

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Phenylketonuria in Minnesota

● Programs ● for ● Detection ● and ● Treatment

ROBERT O. FISCH, M.D.*
EUNICE DAVIS, M.D.**
Minneapolis, Minn.

THOUGH PHENYLKETONURIA has received wide publicity, there are still instances wherein the diagnosis of the disease is made only after the most valuable period for effective treatment has passed. The purpose of this article is to describe briefly the characteristics of phenylketonuria, to discuss several representative case histories of belated diagnosis of the disease, and to explain the facilities that exist in Minnesota for the diagnosis and treatment of phenylketonuria.

This condition was first recognized in 1934 by Dr. A. Folling who discovered that urine of some imbecile children turned green upon the addition of ferric chloride. He demonstrated that the substance responsible for the discoloration was phenylpyruvic acid.[1] Approximately 1% of the residents of institutions for the mentally retarded have been found to suffer from this disease.[2] However, one author has recently emphasized that the incidence of the disease is higher among newborns than can be expected from the data obtained in these institutions.

Heredity

Phenylketonuria appears in children whose parents are both carriers of the phenylketonuric gene. Approximately one fourth of the children in such families are likely to be affected. The phenylketonuric gene is autosomal recessive and not sex-linked.[3] The disease occurs in members of all races, but is most common among western and northern Europeans. It occurs very rarely in Negroes and Semites.[2]

Phenylketonuric babies appear normal at birth but degenerate progressively between four and 24 months of age to the level of moderate to severe mental deficiency.[4] They are generally physically attractive and frequently possess blond hair and blue eyes. They have a tendency toward dermatitis and eczema. About 25% have a history of seizures and almost 80% have abnormal brain waves on electroencephalograph examination.

---

*Assistant Professor, Department of Pediatrics, University of Minnesota.

**Pediatric Consultant, Minnesota Department of Health.

Without treatment, only 1% are likely to have normal intelligence.[5] A considerable number never learn to walk or talk.[6]

In normal people, the level of phenylalanine in the serum is under 3 mg.%, but in phenylketonurics this level may be as high as 60 mg.%.[2] The high concentration of phenylalanine seems to be responsible for the mental retardation of these patients, possibly by direct action on brain cells, or by indirect action through toxicity for various enzyme systems. Phenylalanine is an essential amino acid that constitutes 5% of all proteins in a normal diet. The conversion of phenylalanine to tyrosine is effected by phenylalanine hydroxylase, and the inactivity of phenylalanine hydroxylase is the primary cause of phenylketonuria. The excess phenylalanine in phenylketonurics is excreted in the urine and results in the increased formation of phenylpyruvates and its derivates in the urine.[7]

Screening for Phenylketonuria

Several screening methods for the detection of phenylketonuria are shown; they are comparable in accuracy and each is useful under certain circumstances.

The Diaper Test for Early Detection

The ferric chloride test, one of the oldest and most widely used, consists of the addition of a ferric chloride solution to urine. The diaper test is performed by placing a drop of 10% solution of ferric chloride on the freshly wet diaper.[8] The filter-paper test consists of applying a drop of a 10% solution of ferric chloride to urine dried on filter paper.[9] The Phenistix test is performed by pressing paper strips impregnated with buffered ferric salt against the freshly wet diaper or the urine.[8] The Guthrie test makes use of urine or blood placed in a medium containing bacillus subtilis. The growth of the bacillus is inhibited by the presence of phenylalanine.[10] A series of urine tests is recommended before the infant reaches four months of age.

Tolerance Tests for Carriers

Various methods exist for determining the level of phenylalanine in the serum.[11,12] One of these methods must always be used to confirm a diagnosis of phenylketonuria.[8] Identification of heterozygote carriers is possible by phenylalanine tolerance tests.[13,14]

Specific Therapy

Prophylaxis

The treatment of phenylketonuria consists of putting the patient on a diet low in phenylalanine, a method of treatment first described by H. Bickel in 1953.[15,16] Older children whom he placed on this diet showed certain improvements, but their mental deficiency remained unchanged.[15] Two kinds of prepared formulae are available in the United States — Lofenalac (Mead Johnson and Company) and Ketonil (Merck Sharp & Dohme Company). When a low phenylalanine diet is started in the early months of infancy, mental retardation can be prevented.[17,18]

The Minnesota Program for Detection and Treatment

Programs for the detection and treatment of phenylketonuria were established between 1955 and 1960 in many parts of the United States. During this period, a urine screening program was begun in the Well Child Clinics in Minneapolis and St. Paul. In Minneapolis clinics (operated by the Minneapolis Health Department) approximately 1500 new children are now being screened each year. Since July 1962, all infants born in St. Paul hospitals have been screened for phenylketonuria by the Guthrie test. A nationwide study, under the direction of Dr. Robert Guthrie at the University of Buffalo, has been arranged to evaluate this new test.

Department of Health

Since January 1961, infants born in Clay, Becker, Otter Tail, and Wilkin Counties have been checked in a urine screening program sponsored by the Four-County Project for Retarded Children. The Clay-Becker and Park Region Medical Societies are endorsing this study. The materials used in this screening program are being assembled at the Minnesota Department of Health and are available to hospitals and physicians wishing to conduct phenylketonuria screening. To date, the materials have been distributed to 22 Minnesota hospitals. It is estimated that approximately 25% of the 85,000 infants born in Minnesota each year are included in existing phenylketonuria screening programs.

Positive findings with the urine screening techniques, or the newer Guthrie test, require confirmation by means of a quantitative determination of phenylalanine in the serum. This confirmation may be obtained by sending a specimen to one of several laboratories in various parts of the United States. In Minnesota, the blood specimen may be sent to the Minnesota Department of Health. Specimen containers and instructions are available from the Department of Health and this service is provided as a courtesy.

Department of Pediatrics

Since 1956, an intensive research program studying phenylketonuria has been under way in the Department of Pediatrics at the University of Minnesota Medical School under the supervision of Dr. John A. Anderson, Professor of Pediatrics. In Minnesota, the first serum determinations of phenylalanine were done by the Pediatric Research Laboratory at University Hospitals. This laboratory functioned alone as a detection center until the State Department of Health developed this service. An important achievement of this research program has been the re-evaluation of methods for carrier detection.

Although phenylketonuria can be treated by the family physician, many patients are referred to large centers for prolonged care. Since 1956, one clinic in the Pediatric Outpatient Department of the University of Minnesota Hospitals has been designated for the care of these patients. Children referred to this Phenylketonuria Clinic for treatment are followed by a pediatrician and a dietician. Ordinarily, these children can be treated on an outpatient basis and remain with their private physician for general medical care.

The diet to be prescribed depends on the child's age, the serum phenylalanine level, his mental and physical development, his bone age, and electroencephalographic findings. Counselling is available for parents of phenylketonuric children regarding genetic, educational, and other pertinent aspects of the disease as it involves their family. At present, 26 patients are being actively followed, and some of the children who have been promptly identified and treated are now attending regular classes in the public schools.

Case Reports

Case History—Siblings 1 and 2

A five-year-old male child was referred to a medical clinic on October 21, 1958, because of inability to communicate with other children in kindergarten. The patient had been born following a full-term pregnancy terminating in uneventful delivery. He was sitting up at eight months of age, walking at 14 months, and beginning to talk at four years of age. He had not suffered from eczema, seizures, extreme vomiting, or agitation. He had a three-year-old sister who was normal.

On physical examination, he was found to be an alert child, with blond hair and blue eyes, who spoke very little. The tentative diagnosis was mental retardation of unknown origin. A urinalysis was performed but did not include a ferric chloride test. The child received psychiatric care and later was thought to have infantile autism. His intelligence quotient, according to the Stanford-Binet scale, was estimated to be between 50 and 70.

Meanwhile, the child's mother gave birth to a third child, a female, on November 8, 1958, following a normal pregnancy and uneventful delivery. This child likewise had no history of eczema or seizures; her mental and motor development, however, were slow. She started to sit up at 12 months of age and did not walk until she was 28 months of age. In addition she vomited excessively at increasingly frequent intervals. During October 1962, both children were taken to a pediatrician who noticed the "mousy" odor of their urine and ordered a ferric chloride test. The results of both tests were positive. The doctor's diagnosis of phenylketonuria was subsequently confirmed by the phenylalanine test performed on the blood specimens of both children in the State Health Department. The two children were then referred to the University Phenylketonuria Clinic in July, 1963. At that time the intelligence quotient of the male was 46; that of the female, 70.

If the male's condition had been diagnosed correctly in 1958, his own prognosis would still have been poorer because of his advanced age, but his sister's prognosis would have been considerably better.

After both children had been diagnosed as phenylketonurics, the University Phenylketonuria Clinic kept close contact with their mother during her fourth pregnancy.

The blood of her fourth child, a female, was tested repeatedly in the newborn period (and during infancy) for phenylalanine by the Cooper method and was found to be consistently negative. Had this test been regularly performed on the female during her first few months of life her disease would have been diagnosed sufficiently early to permit normal mental development on a low phenylalanine diet.

Both of these patients manifested slow mental and motor development from birth; both possessed blond hair and blue eyes typical of phenylketonurics, and both excreted urine of "mousy" odor. In spite of these characteristic symptoms, the diagnoses were made late for both children.

Case 3

M.W., a female child, was born January 30, 1962, of her mother's normal third pregnancy. Her two siblings are normal. The neonatal period of the patient was normal and she had no history of seizures, eczema, excessive vomiting, or agitation.

On October 9, 1962, M.W. was taken to the family doctor because of slow development. Although she was eight months old she was unable to sit up and raise her head. Physical examination revealed an appearance of dullness with minimal response to physical stimuli. Otherwise the findings of the examination were within normal range. The results of the ferric chloride and Phenistex tests of the urine were positive. A blood specimen, sent to the State Health Department, was found to contain 30 mg.% of phenylalanine.

On October 26, 1962, the State Health Department referred the baby to the Phenylketonuria Clinic at the University Hospitals. She was found to have light hair and blue eyes and an abnormal electroencephalogram. Her intelligence quotient was between 30 and 40. She was placed on a special diet immediately and her phenylalanine level maintained between 2 and 3 mg.%. She was able to sit up at 12 months of age and showed increased response to her surroundings. Her intelligence quotient on May 20, 1963, was 50 and has increased since. She promises to be of low normal intelligence.

This patient attests the value of prompt communication between family doctor, State Health Department, and University Clinic. The child undoubtedly stands to benefit from the prompt diagnosis and treatment. The question arises, however, why her urine was not screened at six weeks of age.

Case 4

A two-month-old girl, C.B., was referred to University Hospitals with a diagnosis of phenylketonuria. She was born following an uneventful pregnancy and delivery. Her development was normal up to six weeks of age when she was taken to her family physician for a checkup, at which time her urine was found to be positive by the ferric chloride test. A blood specimen was sent to a private laboratory in another state for phenylalanine determination and found to contain 33 mg.%. The doctor then referred the patient to the University Phenylketonuria Clinic.

The family history of this child was negative. The results of her physical examinations were within normal limits. The results of the ferric chloride tests were negative. Blood specimens tested by the State Health Department, as well as by the Phenylketonuria Clinic at University Hospitals, contained less than 3 mg.% phenylalanine. Over a period of three months, repeated tests of blood specimens in various laboratories revealed normal levels of phenylalanine. Correspondence between the Phenylketonuria Clinic and the out-of-state laboratory revealed that there had been an error in calculation and that the actual value should have been computed at 3.3 mg.% rather than 33 mg.%.

In this case the family physician, aware of the importance of the early diagnosis of phenylketonuria, acted promptly. In the future his patients can have the benefit of free and prompt testing of blood for phenylalanine within their own state.

Case 5

J.K., a female patient, was referred to the University Phenylketonuria Clinic at three months of age with a diagnosis of phenylketonuria. After her birth on February 23, 1963, her blood was not tested at the hospital. Her urine specimen, however, was sent to the St. Paul Health Department by her mother on March 23, 1963. It was found by the Guthrie test to contain 12 mg.% of phenylalanine. Her blood specimen was then forwarded to the St. Paul Health Department by her family doctor on April 29, 1963, and found to contain 15 mg.% phenylalanine, again determined by the Guthrie test. Another blood specimen was sent to the State Health Department on May 15, 1963, and found to contain 18 mg.% phenylalanine. Thereupon the child was referred to the University Phenylketonuria Clinic on May 21, 1963.

Two older siblings of J.K. were alive and well by history. The history of her family was negative; the child was said to have been normal in every respect aside from the presence of phenylalanine in the urine and blood. She had no history of seizures, eczema, excess vomiting, or agitation.

Physical examination showed her to be completely normal, with dark hair and dark eyes. All findings were within the normal range. The electroencephalogram showed no abnormality. When tested on May 24, 1963, she showed, according to the Bayley Infant Scale, normal mental and motor development for her age. The results of the ferric chloride test of the urine were negative. The level of phenylalanine in her blood on May 24 1963, was 12.5 mg.%. She was put on a special diet, and by June 4, 1963, the level of phenylalanine had fallen to 2 mg.%.

This patient is particularly interesting because she is a phenylketonuric with a relatively low level of phenylalanine in her blood. Another patient with a similar clinical picture has been described as having "occult phenylketonuria."[19] The case of J.K. attests the value of repeated screenings for phenylketonuria. Because of the early detection of the disease, her prognosis is excellent.

Discussion

Phenylketonuria represents an error of metabolism present at birth, which, if allowed to go untreated, usually results in severe mental retardation. Successful outcome in this disease depends on early diagnosis and prompt institution of a special diet. For optimum therapeutic benefit, the disease should be diagnosed prior to the manifestation of developmental abnormality. For this reason, most successfully treated cases are either diagnosed through the mass screening of infants or through testing the infant relatives of known cases.

Phenylketonuria should be suspected under the following conditions:

1. Whenever an infant's siblings have been found to have phenylketonuria. (The siblings of a phenylketonuric should be repeatedly tested during their first four months of life.)
2. Whenever undiagnosed mental retardation is present in the family.
3. Whenever the patient has manifested slow motor and mental development, or suffered from seizures, eczema, excessive vomiting, or restlessness.
4. Whenever the urine of the patient has an unusually "mousy" odor.
5. Whenever the patient, under one or more of the above conditions, has strikingly blond hair and blue eyes.

Neither the presence nor the absence of any, or all, of the above conditions is conclusive proof of the presence, or absence, of phenylketonuria. The only conclusive proof of the presence or absence of this disease is the determination of the phenylalanine level in the blood serum.

Since many phenylketonurics have no family history of this condition, their disease is not likely to be diagnosed prior to the manifestation of developmental abnormality unless mass screening programs are instituted. A number of techniques for screening programs have been described. However, the results of urine screening tests may be negative if the serum phenylalanine level is less than 15 mg.% at the time of testing. For this reason, it is desirable to screen each child on more than one occasion. A positive or questionable test must be confirmed by quantitative determination of phenylalanine in the serum, since false positives do occasionally occur.

Though treatment cannot be expected to correct a child's mental deficiency in cases of phenylketonuria diagnosed after three years of age, it is still important to detect the disease in an older child so that younger siblings may be subjected to diagnostic testing in early infancy. Siblings of phenylketonurics have a 25% chance of having this disease, and their serum should be tested repeatedly for phenylalanine during the first four months of life. Only a minority of the patients diagnosed through the laboratory services of the Minnesota Department of Health have been sufficiently young to benefit substantially from the prescribed low phenylalanine diet.

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WHAT'S YOUR DIAGNOSIS?

Mr. R. E. V., a twenty-eight year old salesman, was seen in a physician's office for surgical removal of varicose veins. He had had a history of noting a varicose vein of the left leg for at least ten years. Insofar as he knew his parents did not have varicose veins. His general health had otherwise been good. Physical examination demonstrated a well developed, white male in no acute distress. There were large varicose veins of the long saphenous system most prominent in the lower leg. On examination, however, there were also multiple areas of skin pigmentation that were difficult to discern because of the rather deep tan. The right leg by measurement was 1/2" longer and larger in the calf and the ankle than the left although there was no pitting of the skin or tissues. There was a slight increase in warmth. The right foot appeared slightly larger than the left.

What's Your Diagnosis? Turn to page 510.

ROVSING'S SIGN

Pressure exerted over the descending colon producing pain in the right iliac fossa may be positive in acute appendicitis. This is due to the pressure of gas moving toward the cecum and the inflamed appendix.

The Real Tragedy

The tragedy of life is not that people die, it is that they never truly live.
—Dr. Leonard Stidley, Christian Advocate

Iliofemoral Venous Thrombosis

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THROMBOPHLEBITIS INVOLVING the peripheral veins distal to the profunda femoris vein is a rather slowly progressive disease that usually can be halted if the patient is put to bed, his limb elevated, and heparinization begun. If the deep system of veins is involved, pulmonary embolization frequently occurs. Treatment with intravenous heparin will usually prevent this, but should it occur, it is sufficient indication for immediate surgical intervention to prevent further embolization. Ligation of the venous pathway at some judicious proximal point, preferably at the vena-cava level, is the technique of choice. This surgery, although essentially conservative and defensive in nature, carries a significant morbidity if the ligature is placed proximal to the junction of the superficial and deep femoral veins.

When the venous channel proximal to the profunda femoris vein becomes obstructed, a sudden and dramatic change occurs in the patient. He complains of severe pain, and there is an immediate deterioration of his general condition. Cyanosis and engorgement of the tissues is produced by venous stasis and transudation of edema fluid. In instances where the distal venous pressure has been measured under these circumstances, it is often ten times normal.[1] The loss of fluid poured into the affected limb may produce hypovolemia and shock. Careful dissection of such involved limbs following amputation reveals an extensive thrombosis involving even the smallest veins, while the arterial system remains patent. The precipitating factor would seem to be a vigorous vasospasm, for the onset is almost too rapid to incriminate any clotting abnormality. In fact, as in Case 1 reported here, the clotting time is often abnormally long. Frank gangrene will occur in a significant per cent of patients unless effective therapy is instituted. A mortality of 40 per cent and an amputation rate of 50 per cent in the survivors, was reported by Haimovici.[3]

The names ascribed to this syndrome are as numerous as the treatments proposed for it. Phlegmasia Cerulea Dolens,[4] and massive venous thrombosis are most descriptive.[2] Two types of therapy seem most promising: first, interruption of the sympathetic pathways to the limb plus anticoagulation, and second, thrombectomy followed by anticoagulation as proposed by Mahorner.[5] The following cases represent the latter form of therapy.

Case Reports

Case No. 1

A 51-year-old male was admitted to the hospital on September 3, 1963. During the past several months he had been complaining of "ulcer trouble" but otherwise was in good health. Two weeks prior to his admission he developed an aching pain in his left calf, which persisted but was not severe enough to limit his daily activity. During the night prior to his admission the patient was awakened from his sleep by a severe pain in his left leg from his groin to his calf. His leg rapidly became swollen and dusky in color.

Physical Findings

On admission no pulses could be palpated in the left leg and the edema extended to his groin. The limb was not cold, however, and a diagnosis of massive venous thrombosis involving the iliofemoral vein was made. Examination of the patient's abdomen revealed a large nonpulsatile mass occupying the left upper quadrant. Blood studies including platelets and clot retraction were normal; however, the LeeWhite clotting time was 27 minutes. In spite of this the patient was immediately heparinized and his limb elevated. Observation over a two-hour period revealed no improvement and he was taken to surgery.

Operative Findings

Under general anesthesia exploration of the left groin revealed a normally pulsating femoral artery. The vein, however, was distended with clot. A left paramedian incision was made at this time and the abdomen explored. The previously palpated mass rose from the retroperitoneal tissues and involved the aorta with its visceral branches. It did not impinge upon or compress the left iliac vein. A small piece of the tumor mass was excised and interpreted on frozen section as lymphosarcoma.

Treatment

The patient was placed in a reverse Trendelenburg position and occlusive pressure applied to the iliac vein above the palpable thrombus. A thrombectomy of the common femoral vein was then performed, followed by a gush of blood from the distal vein under considerable pressure. All palpable thrombus in the iliac vein was removed with a soft rubber suction catheter, and immediately following release of the proximal iliac vein a free retrograde flow of blood was observed.

The venotomy was closed with a running suture of 5/0 silk. In the immediate postoperative period the patient's pain had disappeared.

Result

Gradually over the next several days the massive swelling receded. He was then given a course of Cobalt 60 therapy to his abdominal tumor. When seen at six weeks, there was only a trace of edema of the ankle and the tumor could not be palpated.

Case No. 2

A 59-year-old female was admitted to the hospital on September 9, 1959. For three days she had complained of aching in her left great toe; then shortly after breakfast on the day of admission her left leg began to swell and became more painful. Further complicating her clinical picture was the presence of a recent left hemiplegia following a cerebral vascular accident and atrial fibrillation which was found on her admission electrocardiogram.

Physical Findings

Examination revealed the leg to be swollen, cool, and cyanotic up to the groin. The femoral pulse on the left was barely palpable and no distal pulses on that side could be felt. All pulses were palpable on the right leg.

Operative Findings

At surgery under spinal anesthesia, the left groin was explored and a swollen thrombosed common femoral vein was discovered. The femoral artery was pulsating normally. By proximal dissection a point on the external iliac vein could be reached where it was soft and no thrombus could be palpated.

Treatment

A twill tape was used to occlude the iliac vein and a thrombectomy of the common femoral vein was performed. A soft rubber catheter applied with gentle suction was used to aspirate as much thrombus as possible. Retrograde flushing demonstrated the patency of the proximal vessel. The thrombus in the distal vein was pulled forth, followed by a gush of free venous flow. Closure of the venotomy was secured with a running suture of 5/0 silk.

Result

In the immediate postoperative period the patient's pain had completely disappeared. During her hospital stay there was prompt and almost complete resolution of swelling in the left leg and she was discharged on October 6, 1959. When seen at six weeks, no swelling was noticed, and on her last clinic visit in August of 1963 both legs were the same size.

Case No. 3

J. B., a 77-year-old male, was admitted to the hospital on April 16, 1963, after being struck by an automobile. He suffered a fracture of both pubic rami on the left. His blood pressure began to fall and with a developing ecchymosis in the perineum it was apparent that there was considerable hemorrhage into the retroperitoneal tissues. Several units of blood were required to stabilize the patient's pulse and blood pressure. During his first four hospital days 4,000 cc. of blood were given. By the twenty-fourth of April, one week postaccident, 5,500 cc. of blood had been given. The patient had had a persistent ileus since admission and had been on nasogastric suction during this time.

Physical Findings

On the twenty-seventh of April a swelling of the left lower leg was noted, which rapidly progressed to involve the entire leg. Warm packs were applied; but because of the recent massive hemorrhage from the pelvis, heparinization was considered too risky, although the diagnosis of deep thrombophlebitis was made. Three days later his pain was more intense, and the leg, which was dusky blue in color, was engorged with edema to the groin. A diagnosis of iliofemoral thrombosis (Phlegmasia Cerulea Dolens) was made at this time and surgery recommended.

Operative Findings

The left groin was explored and the common femoral vein found to be thrombosed. The patient was placed in a reverse Trendelenburg position and a venotomy performed. An adherent organized thrombus was discovered that could be removed only in piecemeal fashion. Further pieces of thrombus were removed from the proximal vein with a soft rubber catheter and suction. The diminished amount of retrograde venous flow, however, was indicative that further adherent thrombus remained in the more proximal iliac vein. Proximal ligature seemed advisable at this point to protect against embolization. Consequently, utilizing a separate right flank incision, the vena cava was identified and doubly ligated below the renal veins.

Results

The patient had a rather stormy postoperative course but was subsequently discharged home with partial weight bearing necessitated by the pelvic fracture. He progressed well and was able to control the bilateral edema with Ace bandages to the mid-thigh. When last seen in August of 1963, four months following surgery, he had only minimal left-foot swelling and no complaints.

Discussion

The results of therapy can be evaluated here both from an immediate and a long-term point of view. The prompt resolution of the swelling, the relief of pain, and the rapid improvement in the patient's general condition tend to support the validity of this method of treatment. Surgery, if necessary, can be performed under local anesthesia and should not add significantly to the mortality. Placing the patient in the reverse Trendelenburg position at the time of venotomy and by compressing the common or external iliac vein above the thrombus whenever possible, the risk of inadvertently releasing a clot into the main venous return to the heart is minimized.

The postphlebitic limb which can result subsequent to the thrombosis is at least partly attributable to the destruction of the deep vein valves which occurs with recanalization of the thrombosed vein. It is hard to imagine that surgical removal of the major offending clot would result in more severe valve destruction than with the use of conservative measures. We believe from our experience that if thrombectomy is to be performed, it should be done early; that is, within the first 48 hours from the time of clinical involvement of the common femoral vein. If more time is allowed to elapse, organization of the thrombus with adherence to the vein will likely occur (as in Case 3) and it will be impossible to leave a clean and glistening intima. In such a circumstance there undoubtedly is a greater propensity to re-thrombosis.

Our long-term care of these patients is patterned after the generally accepted therapy of deep thrombophlebitis, i.e., a minimum of six weeks of anticoagulation, elastic support to the leg or legs up to the knee, and no prolonged periods of sitting.

Summary

Three cases of iliofemoral venous thrombosis are presented in which a thrombectomy was performed with restitution of blood flow. In the two cases where the surgery was performed early there was rapid and apparently complete recovery from this serious process. In the case where surgical intervention was delayed to seventy-two hours a satisfactory complete thrombectomy could not be performed and a vena-cava ligation was deemed necessary with a functional, but less desirable, end result.

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I'm Fine

There's nothing whatever the matter with me;
I'm just as healthy as I can be.
I have arthritis in both my knees;
And when I speak I talk with a wheeze;
My pulse is weak and my blood is thin,
But I'm awfully well for the shape I'm in.

I think my liver is out of whack,
And I've a terrible pain in the small of my back;
My hearing is gone and my vision dim,
Most everything seems to be out of trim.

The way I stagger is a crime,
I'm likely to fall at any time,
Have arch supports for both my feet
Or I wouldn't be able to walk down the street.

My fingers are ugly, stiff at the joints;
My nails are impossible to keep in points;
Complexion is bad, due to dry skin
But, I'm awfully well for the shape I'm in.

My teeth are out, I can't sleep at night;
Memory's failing, heads in a spin.
I'm practically living on aspirin,
But I'm awfully well for the shape I'm in.

Now the moral is, as this tale unfolds,
That for every one who is growing old
It's better to say "I'm fine," with a grin,
Than to tell everyone of the shape I'm in.

Dr. T. H. Lester's mother
Willmar, Minnesota

ANSWER TO WHAT'S YOUR DIAGNOSIS

(From page 506)

Congenital peripheral arteriovenous fistulas with secondary varicose vein formation and secondary increase in size of the extremity.

Memorial Day

Memorial Day weekend will be celebrated as usual by patriotic societies and speeding motorists. Old graves will be decorated; new ones dug.—Changing Times

The Asthmatic Child

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THE INCIDENCE of bronchial asthma in the total population of the United States is approximately 2 to 5%. In children the incidence is about the same; bronchial asthma is a common disease of childhood.

Bray[1] in 1930 estimated that 22% of his cases of asthma affecting children by 10 years of age occurred in the first year of life, and 17% in the second year. Glaser,[2] in reviewing his series of asthmatics, found that 43% developed the disease by two years of age and 87% before seven years of age. It might very well be possible that up to 87% of previously untreated adult asthmatics had their first attack before seven years of age. Some of these adults probably never knew they had asthma at that early age, either because the disease was so mild it was never noticed, or because any physician seen at that time was indecisive and therefore reluctant to make the diagnosis. As asthma in the young can be very serious, a diagnosis should be made if possible and treatment instituted to the best of one's ability.

Differential Diagnosis

In considering the differential diagnosis of asthma, it must be remembered that every patient who wheezes does not have allergic asthma.

Bronchial Asthma

"Bronchial asthma[2] is a form of obstructive emphysema involving both lungs throughout, characterized by paroxysmal attacks of dyspnea, accompanied by wheezing, chiefly expiratory, heard on auscultation of the chest and typically relieved at least in the early stages by sympathomimetic drugs. A continuous asthmatic state may supervene later; but in the beginning, at least, there is always an interval of freedom between attacks."

Retropharyngeal Abscess

The infant under two years of age who presents with wheezing can be a problem in diagnosis; the following common conditions emphasize this fact (Table 1). Mucus in the nasopharynx can elicit a rattling sound that is heard as a transmitted rhonchus on auscultation, but not as an expiratory wheeze.

Retropharyngeal abscess can cause the same sounds, which are exaggerated on bending the head posteriorly.

Congenital Stridor

Congenital laryngeal stridor presents with an inspiratory crow that is evident very early in the newborn. This stridor is increased, along with substernal retraction of the chest, when the baby is excited and at times when feeding. When the baby is sleeping there is usually no sound.

Infectious Croup

Infectious croup also causes an inspiratory crow or stridor sometimes so subtle that it sounds expiratory; hence it is easily confused with asthma. Substernal retraction of the chest is present and should be noted.

Foreign Body

A foreign body in the bronchus is not uncommon. Expiratory wheezing can occur, usually unilateral, and can disappear, reappear, or change intensity from minute to minute or hour to hour. Chest X rays in inspiration and expiration should be taken, especially if the foreign body is nonopaque.

A foreign body in the esophagus can cause both an inspiratory and an expiratory crow and at times dysphagia and vomiting. To rule this out chest X ray and possibly esophagoscopy may be necessary.

Congenital Aortic Ring

Congenital aortic ring is the heart abnormality most apt to imitate asthma; the sounds heard are an inspiratory and expiratory stridor, and there usually is also a history of dysphagia. An esophagram will illustrate this condition readily.

Pertussis

Pertussis with paroxysms of coughing and increased mucous secretions will cause wheezing of short duration. Bacteriologic studies of the pulmonary secretions and evidence of marked lymphocytosis in the peripheral blood help to differentiate.

TABLE I

Differential Diagnosis of Asthma Under Two Years of Age

1. Mucus in the nasopharynx
2. Retropharyngeal abscess or enlarged adenoids
3. Congenital laryngeal stridor
4. Infectious croup
5. Foreign body in the bronchus
6. Foreign body in the esophagus.
7. Congenital aortic ring
8. Pertussis
9. Cystic fibrosis of the pancreas.
10. Pneumonitis or bronchiolitis.
11. Agammaglobulinemia.

Cystic Fibrosis

Cystic fibrosis of the pancreas is most important because of recurrent wheezing and respiratory infections. Usually gastrointestinal symptoms are also present. To make matters more difficult, the incidence of allergy in these patients is much higher than in the normal population, and therefore asthma can actually coexist. Simple screening tests and determination of elevated sweat electrolytes will rule out this disease.

Pneumonitis

Pneumonitis and bronchiolitis present the greatest difficulty in diagnosis, as the wheezing and appearance of the patient more closely imitate asthma than any of the other conditions, the reason being that both show obstruction of the lumina of the small bronchi and bronchioles. In the allergic state this obstruction is caused by edema of the mucosa, smooth muscle spasm, and increased secretion of mucus; while in bronchiolitis there is an inflammatory infiltrate in the lumina and bronchiolar mucosa.

Probably the simplest way to resolve the diagnosis is to use a therapeutic test by giving a small injection of epinephrine. Should there be an adequate response, asthma is most likely present. However, there are times when a bronchiolitis will respond to epinephrine, due to the fact that both diseases exist together, the respiratory infection having precipitated the asthma.

There is also some evidence that bronchiolitis might initiate or prime an allergic state. Glaser and Wittig[3] studied 100 patients in retrospect who had had bronchiolitis. Their ages were four weeks to four years, 76% being under one year of age. Of this group 49% developed allergic respiratory disease, 32% asthma, and 17% nasal allergies (perennial allergic rhinitis and hay fever). A reliable family history was obtained for 83 patients and was positive for allergy in 44%.

The very young patient with agammaglobulinemia can have recurrent respiratory infections with wheezing; the serum gamma globulin level being very low will differentiate.

There are many more conditions in the differential that could be mentioned, but they rarely occur; if these common conditions can be kept in mind, diagnosis will be less difficult.

Etiology

There are three etiologic factors that are important: foods, inhalants, and respiratory infection.

Foods

Foods are significant in the very young. Egg, cow's milk, and wheat are the most common offenders. Egg-white has special significance because it is the one single greatest cause of infantile atopic eczema. Also, it is well documented that eczema in infancy is very often followed by asthma in later childhood; figures quoted in the literature state that from 30 to 66% of eczemas progress to asthma. Buffum[4] found that babies with asthma, eczema, and positive skin test to egg-white had very serious asthma, with poor prognosis for early recovery. In later childhood foods become less significant.

Inhalants

Inhalants which are the most common sensitizers in the infant are house dust, molds, and animal danders. In the older child pollens become important in addition to the other inhalants.

Infection

Infection in the form of an acute respiratory infection (viral or bacterial) has always been a controversial point. It has been generally accepted by allergists that infection acts as a trigger mechanism, which, when added to etiologic factors such as foods and inhalants, precipitates an attack of asthma. Others say that the infectious agents sensitize the bronchial mucosa, thereby causing the attack. Because of this difference of opinion, many descriptive terms have evolved, such as asthmatic bronchitis, infectious asthma, intrinsic asthma, and asthmatoid bronchitis. Freeman and Todd[5] have attempted to clarify this by determining whether or not wheezing, which occurred with a viral respiratory tract illness, was associated with an allergic state. They reported on a retrospective study of the records of 357 children with respiratory illness due to parainfluenzal virus, respiratory syncytial virus, or adenovirus. It was found that 27% of all the children had wheezing, which was three times more frequent in those children with allergy; also, wheezing was more frequent with respiratory syncytial virus, or adenovirus. It was found that 27% of all the children had wheezing, which was three times more frequent in those children with allergy; also wheezing was more frequent with respiratory syncytial virus infection (52%), involving mostly young infants. Bronchiolitis has been significantly associated with this virus. The incidence of wheezing with a specific virus infection was highest (41%) among infants under 12 months of age. Allergy was more frequent in children who wheezed with their virus infection (50%) than in those who did not (17%). However, wheezing was less frequently associated with allergy below the age of 18 months (39%) than above this age (73%). It was suggested that recurrent wheezing with respiratory tract infection or asthmatic bronchitis is, at least in part, a preallergic or allergic state. This point has also been documented by others.

Physical Examination

There is a difference in the physical findings between the infant up to two years of age and the child from two to seven years of age and up (Table 2). Both age groups are very dyspneic. The infant breathes comfortably when lying on his back, but the child must sit propped up. Anxiety in the child is marked but of no consequence in the infant. Marked emphysema is present in the infant — so much so that cardiac dullness cannot be elicited at times when percussing the chest. Emphysema in the child is not so marked. Expiratory wheezing is always present in the child; but many times in the infant hardly any air exchange is discernible, due to the marked emphysema. More often than not, there is lowgrade fever in the infant.

It should be mentioned that in the infant under six months of age wheezing can be far from characteristic; it is actually not a wheeze but a rattly-sounding respiration, probably produced by air in the tracheobronchial tree rushing back and forth over increased mucous secretion through a fairly adequate airway. When the caliber of the lumina is further narrowed by spasm of the smooth muscles and edema, the characteristic wheeze is heard.

TABLE 2
Physical Examination of the Infant and Child

Age Years	Dyspnea	Expiratory Wheeze	Emphysema	Cardiac Dullness	Anxiety	Position	Fever
Infant to 2	Marked	Minimal at times	Marked	Often not present	None	Comfortable lying on back	Low grade
Child 2 to 7	Marked /	Marked	Moderate	Present	Marked	Sitting propped up	Usually none

Treatment of the Acute Attack of Asthma

In treating the acute attack of asthma bedrest is most important, because decreasing physical activity reduces respiratory effort. Administration of a sympathomimetic drug as soon as possible after the onset of the attack is desirable.

Epinephrine

Epinephrine, aqueous 1:1000 in a dose of 0.20 cc. given subcutaneously at an interval of 15 to 30 minutes until relief is obtained, is the best treatment. If there is no improvement after three doses, no more should be given, as the patient will not respond. To maintain the effect of the aqueous epinephrine which is short-acting, a long-acting type should be given 15 to 30 minutes after the dose of aqueous drug that gave relief. Sus-phrine (Brewer), which is an epinephrine suspension 1:200, can be used. The dose is 0.10 to 0.30 cc. subcutaneously; 20% of this drug acts quickly and the rest over a period of four to six hours. If this is not available, aminophylline orally or by rectum, with or without ephedrine and a barbiturate, can be substituted. Epinephrine works best when given early in an attack and in small frequent doses.

When an oral sympathomimetic such as ephedrine is used, it can be combined with aminophylline. There are a great number of preparations available which contain these drugs with the addition of a sedative to decrease the side affects of the ephedrine. If nausea or vomiting is present, then aminophylline or theophyllin suppositories can be used; but when giving these drugs by rectum to infants and children, the dose must be carefully calculated. A safe amount is 5 mg/kilo per dose, not to be given at intervals of less than eight to 12 hours, and only when necessary. Toxic reactions can be very severe, starting with nausea and vomiting, then severe cerebral stimulation, and finally coma and death. Blood levels of aminophylline administered by rectum can be as high as when given intravenously; when given frequently by rectum, however, there is a cumulative effect of the drug. Also, one cannot predict blood levels in any individuals, as there is extreme variation.

Contraindicated

Antihistamines are never used in treatment of acute attacks of asthma because they have an atropine-like action. They tend to dry the mucous secretion, thereby increasing the pulmonary congestion.

Corticosteroids are not indicated in the treatment of the acute attack of asthma because they take about three to six hours to produce any effect. They should not be used for only a dose or two; therefore once they are given, the physician is committed to prescribe adequate dosage and to be prepared to give the drug for short-term treatment of about a week or two. The patient should never have access to this drug or be allowed to prescribe for himself. He should know he is receiving or has received corticosteroids. If he is confronted with a stress situation within six months of receiving the drug, he will need it again; therefore whoever is treating him should be informed.

Cough Mixtures

When the acute wheezing and dyspnea have subsided, cough mixtures containing ephedrine and an antitussive drug should be used to decrease coughing but not eliminate it. Excessive coughing precipitates more wheezing. Also, since there are increased mucous secretions with a tendency to dry, an expectorant can be given to keep them so liquid that they can be raised with a minimum of coughing. The iodides can be used, or if there is a sensitivity to these, glyceryl-guaiacolate can be used. As prolonged use of iodides can lead to goitre and myxedema, this must be watched; in fact, rotation of expectorants might well obviate this hazard.

Status Asthmaticus

There are patients who do not respond to treatment. The child who has been wheezing for a varying period of time and does not respond to epinephrine or any of the other antiasthmatic drugs, is in status asthmaticus. He is usually very dehydrated as he declines liquids because of nausea and vomiting; in addition, there is an insensible loss of water from increased respirations and fever, if present. His pulmonary secretions are dry, viscid, and inspissated in the small bronchi and bronchioles. Because of this pulmonary stasis, he has infection, all of this adding up to a sick infant or child who needs emergency treatment.

A patient with status asthmaticus should be hospitalized as soon as possible, as he is usually anoxic and needs humid oxygen. Hydration is begun by using intravenous fluid as one would treat any dehydrated child. This is really the most important part of treatment, as in this way, the inspissated secretions are liquified and loosened to relieve obstruction of airways and any electrolyte imbalance corrected. Intravenous aminophylline can be added to intravenous fluid in a dose of 5 mg/kilo and allowed to run in slowly — to dilate the small bronchi and bronchioles. Corticosteroids are definitely indicated and are given intravenously. Hydracortisone (Solu-cortef) can be used in stress dosages of 200 mg/m^2/24 hours at six-hour intervals. These drugs are given for their anti-inflammatory effect, which does not occur, however, for from three to six hours.

On admission to the hospital, a chest X ray is done to note any pneumonic infiltration or atelectasis. Parenteral antibiotic is given for infection and mild sedation to lessen anxiety.

After treatment is begun it may take anywhere from six to 36 hours for improvement. If the patient gets worse, further X rays of the chest should be done and bronchoscopy considered. When improvement becomes evident, corticosteroids are given orally and intravenous fluids stopped. Other therapy from then on is the same as for the subsided acute attack of asthma.

Follow-up Treatment

Any infant or child, who has had more than one attack of asthma that has responded to treatment with antiasthmatic drugs, deserves to have as complete an allergic study as possible, including a detailed clinical and allergic history covering foods and environmental conditions. Laboratory tests such as cytologic examination of nasal and pulmonary secretions and skin tests should be made. Tests to be applied are selected on the basis of the clinical history. Skin tests are important, and along with all the other laboratory tests, confirm clinical impressions; in this way a specific etiologic factor can be found that might lead to specific treatment. It should be mentioned that adequate and reliable skin tests can be done on small infants under a year.

When the study is complete, detailed instructions are outlined and environmental control is emphasized. In addition, when specifically indicated by correlating clinical history and skin tests, desensitization should be considered. Many allergists agree that this can be successfully done at one year of age and under; others start after one year. In my experience it can be done under a year, especially for infants sensitive to house dust.

Prophylaxis of Asthma

The general practitioner and pediatrician have a great opportunity to practice prophylaxis, especially on children from allergic families. Infants from families where one or more parents or siblings are allergic have a 60% chance of developing a major allergy such as eczema, hay fever, perennial allergic rhinitis, or asthma by the age of six years. Glaser[2] has shown that 80% of infants who have eczema will develop a major respiratory allergy by 10 years of age. He considers cow's milk a very allergenic food for an infant from a highly allergic family; therefore a newborn baby from such a family should be breast-fed because it has been shown he will have a seven times better chance of avoiding eczema than if he is fed cow's milk. If the baby cannot be breastfed, Glaser advises using a substitute such as a soybean formula right from birth. In this way the incidence of eczema is lowered, and thereby the percentage chance of developing a respiratory allergy such as asthma.

In the United States, ragweed pollen can be considered the one single greatest cause of asthma, seasonal in nature, and is usually preceded by one season or more of hay fever alone. However, the asthma will often be the only manifestation during the hay-fever season, and it may even precede hay fever.

Children with hay fever, who have had no treatment such as desensitization with a pollen extract, have a greater chance of developing seasonal asthma, as figures show that 40 to 60% of hay-fever patients will develop asthma if untreated, and undoubtedly a certain percentage of these will proceed to become chronic asthmatics. On this basis it would be advisable that all hay-fever patients be desensitized.

Course of Asthma in Children

The course of asthma in infants and children is very difficult to assess. In fact there are many who say that all children outgrow asthma; others say they never do. Rackemann and Edwards[6] in 1952 reported a follow-up on 688 treated asthmatic patients after an interval of 20 years. One group of 449 had been seen before age 13 and another group of 239 after this age. Of the children seen before 13 years of age, 75% no longer had asthma in their teenage years; 15% had mild asthma; 10.9% had serious asthma, and four had died. The group over 13 years of age had more serious asthma: of 239 patients 21.7% were free of asthma; 25.5% were relieved; 8% had no asthma but other allergies; 12.1% had mild asthma; 44.7% had severe asthma; and six had died from asthma.

Dees[7] followed 233 asthmatic children under 14 years of age during the first five years of the pediatric allergy clinic at Duke. As reported in 1957, 44% had essentially no asthma after two years' treatment. Moderate asthma was present in 36%, and severe asthma was still a problem in 20%. All these patients are still being followed.

Untreated asthmatics are practically impossible to follow, the reason being that they are very mild cases, probably never seen by a physician; or if they are seen, the physician may not recognize that they have asthma. Therefore, without knowing they have the disease, they learn to live with their problem, because they think it is normal. It is only when there is marked difficulty in breathing and they become apprehensive that medical aid is sought. We can only speculate as to what happens to these individuals. They could account for the greater number of severe chronic asthmatics with emphysema that occur in adulthood.

Conclusions

Asthma is a common disease in infants and children and can be serious. Not all patients with wheezing have asthma. The differential diagnosis and the treatment of the acute attack of asthma and status asthmaticus for infants under two years should be accurately evaluated.. Prophylaxis of asthma can be carried out on infants from highly allergic families, and also on hay-fever patients. Infants and children do not have a good chance of outgrowing asthma without adequate treatment.

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ALBRIGHT'S SYNDROME

(Polyostotic Fibrous Dysplasia)

This syndrome may be discovered because of incidental or accidental finding of fibrous dysplasia of the bone or because of sexual precocity or because of brown pigmented areas of the skin which may be observed in the course of a routine check-up. The syndrome is usually observed in children or young adults, predominantly in females. Hereditary factors may account for the bone cysts.

The multiple bone cysts consist of fibrous dysplasia which replaces the medullary structure. It is found more often in pelvic bones and the bones of the lower extremities. On occasion it may not be recognized until a pathologic fracture has occurred in childhood or early adult life.

The accompanying areas of cutaneous pigmentation vary in size from freckle-like birthmarks to large, flat, brown patches. The degree of pigmentation signifies the extent of skeletal involvement.

The endocrine features consist of unusual sexual precocity in the female with early onset of menstrual cycle, enlargement of breasts, and development of adolescent external genitalia. The 17-ketosteroid values are normal.

It may be necessary to differentiate this condition from hyperparathyroidism in which the bone lesions are generalized, whereas in Albright's syndrome a considerable portion of the skeleton is usually unaffected.

Durham-Encyclopedia of Medical Syndromes
Hoeber, Inc., New York

Galen's Materia Medica*

For Facial Neuralgia

For pain on one side of the head or face smear with fifteen earthworms and fifteen grains of pepper powdered in vinegar.

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*Thorndike, Lynn — see Minn Med Oct. '63.

One Thinking

If you find 100 men in complete agreement, you can bet your bottom dollar that 99 of them are doing the agreeing, and one is doing the thinking.

—Lyndon B. Johnson

Most of us could pay as we go if we didn't go so much.—Herbert Prochnow

Acute Abdominal Trauma[**]

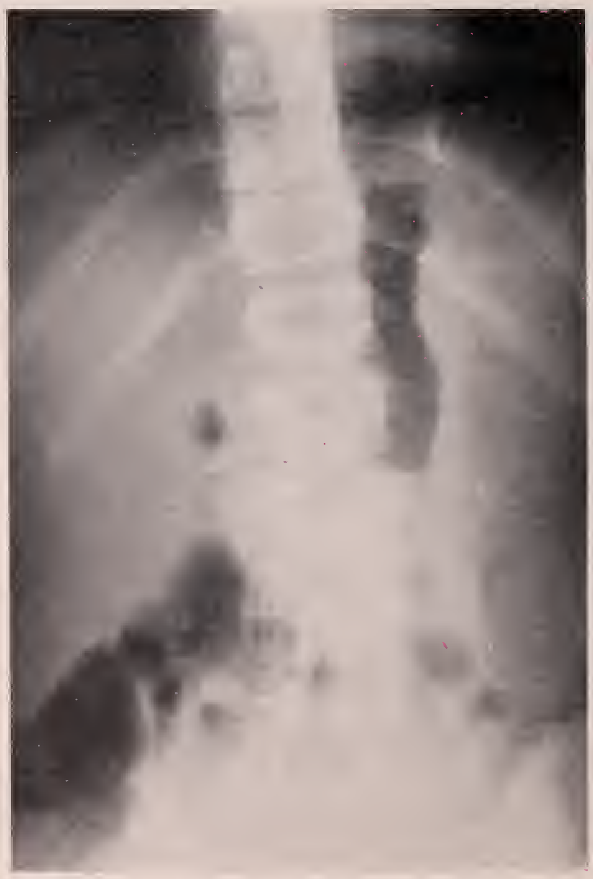

Fig. 1 — Medial displacement of gastric air bubble by hematoma from ruptured spleen.

It is not possible in a short paper to cover all aspects of the subject of abdominal trauma. The following remarks are confined to a few of the diagnostic and therapeutic problems encountered in the management of such injuries. It is suggested that in surgical treatment precise repair of damaged organs and meticulous hemostasis be practiced with little reliance on external drainage.

As a general rule, penetrating wounds of the abdomen pose little problem in diagnosis since almost without exception patients with such injuries are operated upon. Except for those individuals with minor scratches and lacerations in whom it is obvious that the abdominal cavity has not been entered, patients with penetrating wounds of the abdomen are explored.

Blunt Trauma

Abdominal injuries due to blunt trauma pose a considerably more complex situation. The diagnosis may be immediately obvious

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[**] Presented at Continuation Course in Surgery, University of Minnesota Medical School, May 18, 1963.

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from the signs and symptoms and there may be no difficulty in arriving at a decision to explore the abdomen. On the other hand, the picture may be less clear-cut. Several situations which may be encountered are worthy of brief comment.

X ray of Abdomen

When abdominal injury is suspected, X-ray studies should be carried out to determine the presence or absence of free intraperitoneal air, as the demonstration of such free air is pathognomonic of perforation of a hollow viscus and requires operative treatment.

Hypotension

Otherwise unexplained hypotension in a patient with minimal abdominal signs or in a comatose patient whose abdominal signs cannot be properly evaluated may dictate the necessity for laparotomy. In patients with fractures or chest injuries, it may be extremely difficult to decide whether the hypotension is due to these injuries or to bleeding within the peritoneal cavity. If shock from blood loss is not adequately ex-

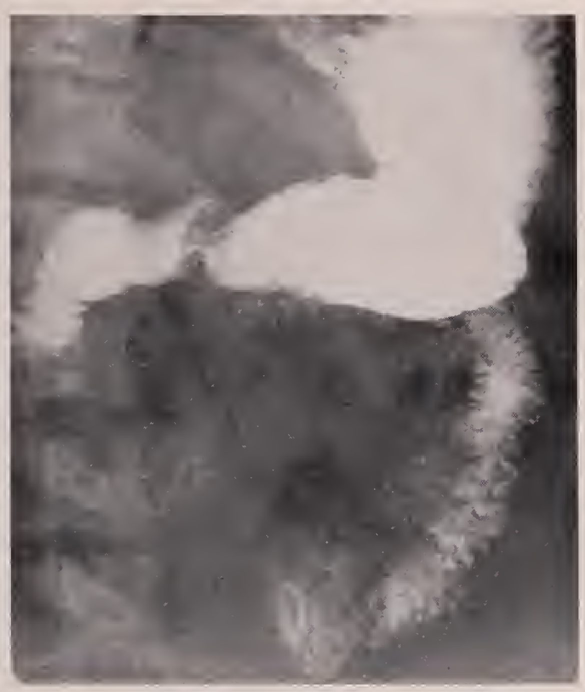

Fig. 2 — Upper gastrointestinal X-ray examination of a patient with recent abdominal trauma. No extravasation of contrast material is evident.

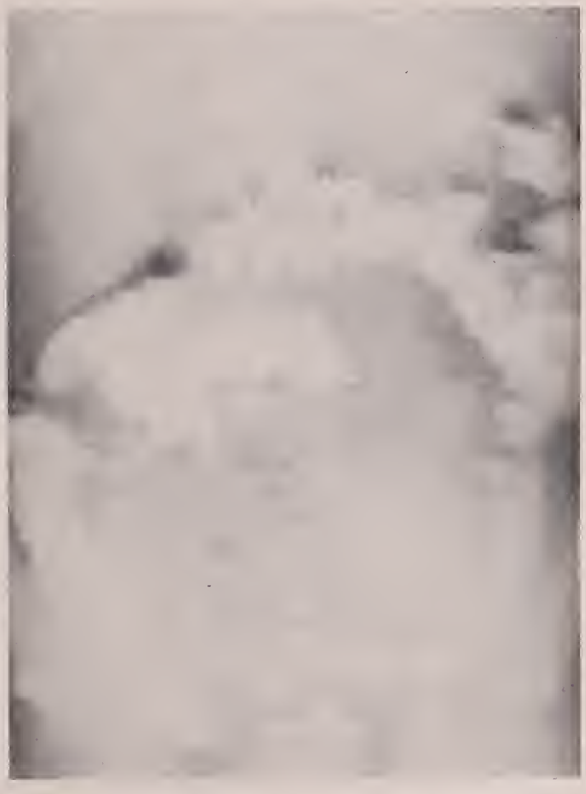

Fig. 3 — Delayed film of the same patient shown in Figure 2. The extravasation of contrast material into the retroperitoneal area from ruptured duodenum is apparent.

plained by obvious injuries, it may at times be necessary to explore the abdomen.

The Nature of the Injury

One may suspect abdominal visceral injury from the nature of the trauma. For example, fractures of the lower ribs on the left are associated in a high percentage of instances with traumatic rupture of the spleen; patients with such an injury have suffered a violent blow and must be observed carefully and closely for splenic injury. In similar fashion patients with fractures of the lower ribs on the right, especially if associated with right-sided fractures of the ilium, frequently have liver injuries. The combination of osseous injuries of this variety is again an indication of a severe traumatic episode and such patients should be carefully observed for signs of visceral injury. Similarly, patients with lower rib fractures of either side may have suffered renal injury. Pelvic fractures are associated with bladder injury in a significant number of patients, and such injury should be suspected when pelvic fractures are demonstrated. In many patients visceral injury may become obvious only from repeated abdominal examinations whereby there is demonstrated increasing abdominal distention, tenderness, or rigidity with or without an associated drop in hemoglobin or an increasing leucocytosis.

Specific Visceral Injuries

Spleen

Injuries of the spleen may be suspected from characteristic rib fractures, hypotension, leucocytosis, and/or abdominal tenderness, but all or part of these signs may be absent and the diagnosis may not be obvious. In such circumstances when splenic rupture is suspected and where abdominal X rays have shown no free air to indicate other visceral injury and the signs and symptoms are insufficient to warrant abdominal exploration, a policy of watchful waiting is adopted. The most useful laboratory test has been the repeated determination of hemoglobin at four-hour intervals. It may be necessary to carry out such hemoglobin measurements over a period of several days before the characteristic drop in hemoglobin indicative of continued bleeding or rebleeding from the lacerated spleen occurs. In our experience, such a policy of observation has not been associated with an increased mortality rate.

Abdominal taps have not provided uniformly useful information. Several patients subsequently shown at operation to have a rupture of the spleen and hematomas localized to the splenic fossa have previously had negative abdominal taps. This procedure might provide a diagnosis in a higher percentage of cases, if a polyethylene tubing were introduced through the abdominal paracentesis needle and the patient turned in several positions during aspiration. We have thus far, however, had no experience with this modified procedure.

Radiographs may be helpful in some patients with splenic rupture in whom the diagnosis is not clear from the clinical picture. As shown in Figure 1, displacement of the gastric bubble by a hematoma in the region of the spleen may add evidence to the diagnosis of splenic rupture. In patients where the stomach appears to be pushed away from the diaphragm, the introduction of barium meal into the stomach may be utilized to confirm displacement of the stomach. It should be emphasized, however, that the absence of an opaque mass in the left upper quadrant does not rule out rupture of the spleen. Gas-filled viscera may be seen in the X ray to be in close approximation to the diaphragm and a rupture of the spleen still be present.

Splenic laceration or rupture is treated by splenectomy, care being exercised that the tail of the pancreas is not injured and that no oozing vessels are left in the splenic fossa. Drainage is not employed.

Liver

Injuries of the liver may be manifest by abdominal signs such as tenderness and rigidity and by shock due to blood loss.

In the management of liver injuries the goal of surgical repair should be water-tight closure of the injured area and the prevention of leakage of bile and blood in the postoperative period, rather than acceptance of leakage as inevitable. Lacerations of the liver are repaired by suture. If there is extensive damage to a lobe it should be removed with water-tight closure of the remaining liver parenchyma at the site of resection. In all but the most minor tears of liver substance, T-tube drainage of the common bile duct should be provided as well. Free egress for bile without pressure is provided, thereby reducing chances of leakage from the suture line. In the rare instance where diffuse pulping of the liver has occurred, water-tight repair is not possible and a compromise must be made. In addition to T-tube drainage of the bile duct, external drainage is provided. Large bore catheters placed in the subphrenic space and attached to suction should be utilized instead of Penrose drains. In repair of the great majority of liver injuries not of this character, careful suture closure of the defect and T-tube decompression of the common duct render attempts at external drainage by Penrose drains unnecessary.

Pancreas

Pancreatic injuries are often missed unless laparotomy is carried out because of injury to other organs; the diagnosis may first be made when a pseudocyst appears. As in the liver, the treatment of injury of the pancreas in the acute phase requires water-tight closure of the gland and decompression of the duct system to provide free egress of pancreatic juice. Injury to the body or tail of the pancreas, if extensive, should be treated by resection of all pancreatic tissue damaged and beyond, including the tail, ligation of the pancreatic duct at the level of gland section, and tight closure of the remaining pancreatic parenchyma. If the injury involves the head of the pancreas and does not lend itself to resection, suture closure of the pancreatic capsule as completely as possible is accomplished and transduodenal spincterotomy carried out. A small polyethylene tubing is passed into the main pancreatic duct for decompression and brought out through the duodenal wall and to the skin by means of a Witzel enterostomy. Decompression of the pancreatic duct is thus provided and leakage into the peritoneal cavity from the area of injury minimized. The polyethylene tubing is easily removed when healing is complete. External drainage with Penrose drains is not utilized.

Intestinal Tract

Diagnosis of injury to the hollow viscera may be suspected from abdominal symptoms and signs. If free intraperitoneal air is demonstrable by X-ray examination the diagnosis is confirmed. A lateral decubitus or upright abdominal film is necessary to demonstrate free intraperitoneal air; the former is usually more easily obtained in the severely injured patient. Perforations including those of the colon are closed by suture and after peritoneal lavage, closure of the abdomen without drainage is accomplished. When colon injuries are treated more than 12 hours following injury or when associated with massive contamination or extensive injury to the bowel a colostomy may be required. However, the majority of colon wounds and lacerations otherwise are amenable to primary closure by suture. The problem is not the same as that encountered in the military, since the perforations encountered in civilian experience usually occur as a result of puncturing injuries or by missiles of low velocity. Observation of the patient by the original surgical team in the postoperative period is also possible. All these factors make for greater latitude in choice of operative treatment in colon injuries in civilian practice.

One aspect of injury of the hollow viscera which may be a problem in diagnosis is that of retroperitoneal rupture of the duodenum without perforation into the free peritoneal cavity. In patients with blunt abdominal trauma who have failed to recover properly following injury with persistent low grade fever, leucocytosis, or abdominal tenderness, but whose clinical signs have never been enough to warrant laparotomy, this condition may be suspected. An upper gastrointestinal X ray may be of benefit to demonstrate a retroperitoneal duodenal tear. The value of a delayed film in diagnosis of this injury can be shown. Whereas a normal pattern of duodenal mucosa is apparent in the upper gastrointestinal X ray shown in Figure 2, a delayed film (Figure 3) shows extravasation of the contrast medium due to a retroperitoneal duodenal tear.

Kidney

Renal injury may be suspected from physical signs or from the nature of the trauma (e.g., fracture of lower ribs or the transverse processes of lumbar vertebrae) or the presence of hematuria. In patients suspected of such injuries, intravenous pyelography will provide a diagnosis. This procedure can be carried out as a bedside diagnostic study (Figure 4).

Pelvic Fractures

Pelvic fractures present several problems in abdominal trauma. They may or may not be associated with bladder rupture. Cystograms, which can be done as a bedside procedure, will demonstrate such bladder injuries; Figure 5, showing a bedside cystogram, demonstrates rupture of the bladder with free extravasation of the contrast agent into the peritoneal cavity. Pelvic fractures are often associated with extensive bleeding both into the retroperitoneal tissues and into the peritoneal cavity as well. Shock may be extremely difficult to control in patients with extensive pelvic fractures, and it may at times be difficult to determine if bleeding is due to the pelvic fracture alone and not the result of intra-abdominal hemorrhage from a visceral injury as well. In pelvic fractures associated with rupture of the bladder, operation is of course required. In some other instances, it may be necessary to explore patients to determine whether or not the source of shock and hemorrhage is due entirely to the pelvic fracture or to an associated intra-abdominal visceral injury.

Diaphragm

Traumatic diaphragmatic hernia occurs with sufficient frequency to warrant consideration in any patient with a blunt injury of the abdomen. Delayed diagnosis is often lethal, whereas prompt recognition of this condition is associated with recovery in a high percentage of cases. The diagnosis may

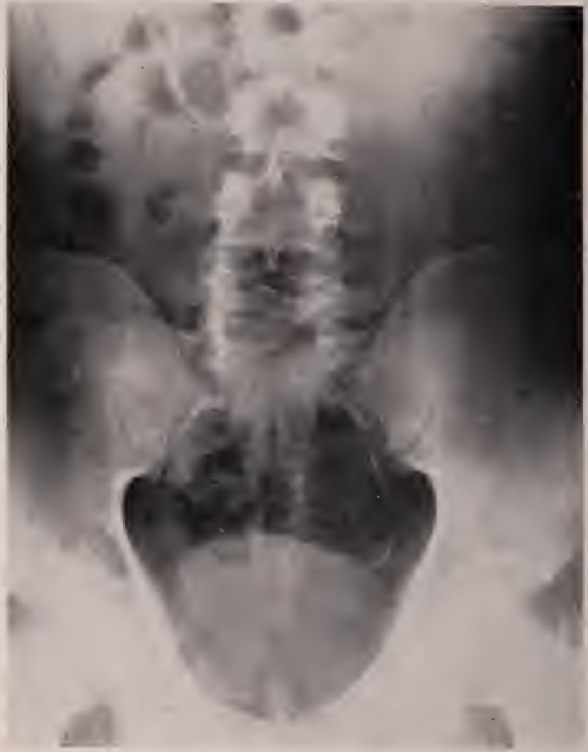

Fig. 4 — Intravenous pyelogram showing rupture of the left kidney and extravasation of contrast material.

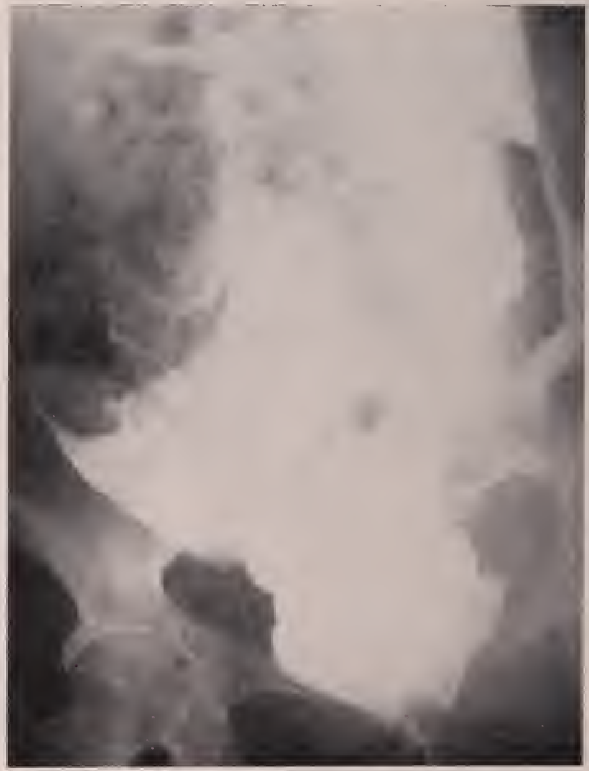

Fig. 5 — Bedside cystogram of a patient with pelvic fracture. The intraperitoneal rupture of bladder with extravasation of contrast material is apparent.

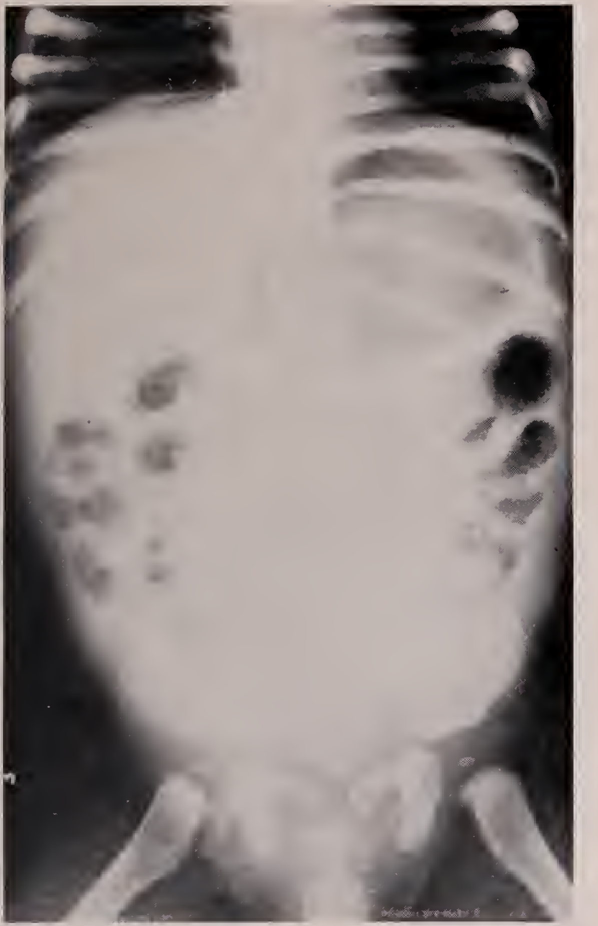

Fig. 6 — Supine abdominal X ray of a child who was shown to have a ruptured small intestine at operation. Old, healing fractures of 11th and 12th ribs are apparent.

be apparent from a chest X ray showing viscera in the chest cavity or may be made from thoracentesis of an apparently blood-filled hemithorax, if material resembling gastric juice or small bowel content is recovered thereby. Simple laboratory tests for acid and bile will confirm the finding. The diagnosis may be delayed and first become apparent at a remote date following trauma, when an upper gastrointestinal or colon X-ray study shows abdominal viscera within the thorax.

Battered Child Syndrome*

An occasional young child with abdominal distention, tenderness, and/or rigidity will be found by X ray to have free intraperitoneal air, and a ruptured viscus on abdominal exploration. A history such as one of falling out of bed or other story incompatible with the findings has usually been obtained preoperatively, but later investigation has shown the child to have been beaten by a parent. Often such children have demonstrated other evidences of injury on physical and radiographic study, such as multiple bruises and healing fractures (Figure 6).

Summary

Abdominal injuries due to blunt trauma may be suspected from the characteristic symptoms and physical findings or from the nature of osseous injuries.

If X rays are unrevealing and the signs unclear, the best aids to diagnosis are frequent examination of the abdomen and repeated hemoglobin determinations.

Laparotomy may be necessary to rule out visceral damage or to determine if there is such injury in patients with pelvic fractures.

Emphasis should be placed on meticulous hemostasis and careful precise closure of tears and lacterations of pancreas and liver as well as hollow viscera. Splenic injury is treated by splenectomy. In the pancreas and liver decompression of the secretory ducts of the organ are necessary as well. There are few, if any, indications for Penrose drains if abdominal injuries are treated early and correctly. Extensive hepatic trauma may preclude exact suture repair or resection, and a compromise procedure must be accepted. T-tube decompression of the bile duct and large suction catheters in areas of hepatic injury are utilized under these circumstances.

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*See Minnesota Medicine 46:977, 1963.

Many Try It

If you want to go through life completely misunderstood, say exactly what you mean.—S. J. Mann

The Bezoar Stone

If you were a European living during the superstition-ridden and fraud-gullible 15th century and you had accidentally ingested poison, your antidote would be to swallow a bezoar stone, so-named for its Persian derivation: "expel poison."

Just as exquisite pearls are the morbid secretions of sick oysters, so bezoar stones were disease concretions formed in the intestines of sick goats — though legend tried vainly to glamorize their origin by representing them to be the crystallized tears of deer suffering the pangs of indigestion after perversely eating black snakes.

If swallowing a stone reputed to be a bezoar stone failed as an antidote, then that particular stone was "spurious'" and was discarded as a "fake." Such an instance, however, in no way impugned the efficacy of the "genuine" bezoar stone. The validity of a single stone could be questioned, but not the principle underlying its application.

In these earlier eras there were other prevailing delusions about stones, especially semiprecious and precious ones. For example, "in bygone days, agate cured the bite of spiders, stopped the pain of headaches, and arrested the bleeding of wounds. Beryl, when swallowed, healed quinsy and, when pressed on the lids, cured disease of the eyes. The carbuncle worn about the person brought relief from worry and freedom from mental disease. Coral drove off malarial fever and, set in the collar of a dog, prevented madness. Red coral worn about the neck changed its shade with the state of the wearer's health. The diamond cured malaria and, swallowed as a powder, was supposed to be a poison — which it is not. The emerald suspended from the neck warded off convulsions; tied to the ankle of a woman, it assured an easy childbirth; and swallowed, it cured dysentery. Powdered jade relieved heartburn, and jasper cured heart-disease. The sapphire was a remedy for typhoid fever and snake-bite. The topaz assured a long and healthy life, beauty, and intelligence. Pearls dissolved in wine were a potent remedy against the remaining ills to which the flesh is heir. Jewels were plentiful, and sickness vastly prevalent."*

Even today a few quaint superstitions persist. Some people are still intrigued by the idea of their birthstones bringing them good luck; and a few still believe that an opal possesses the uncanny and elusive property of reflecting the well-or-ill-being of its wearer.

Naturally and fortunately the bezoar stone is no longer used as an antidote, nor is it even available for purchase. However, it can still be seen occasionally in museums — as a curiosity and a reminder of man's colossal credulity.

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*Haggard, Howard W., M.D.: "The Lame, the Halt, and the Blind," p. 80.

It's probably even later than the fellow who says it's later than you think thinks it is.
—Cincinnati Inquirer

My son, if sinners entice thee, consent thou not.—Proverbs 1

Narcotic Withdrawal Syndrome

Suppression
of
by
Means
of

Electric
Convulsive
Therapy

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WHENEVER OPIUM OR any of its habit-forming derivatives are abruptly withdrawn from an addicted person a definite train of symptoms known as the abstinence or withdrawal syndrome occurs. If within 12 to 14 hours after the last dose it is not repeated, rhinorrhea, lacrimation, perspiration, and sneezing appear as the early symptoms. As these gradually increase in severity, anorexia, mydriasis, tremor, and "gooseflesh" are added. About 36 hours after the last dose uncontrollable twitchings of the muscles appear together with cramps in the legs, abdomen, and back. The patient becomes extremely restless, develops insomnia, and both the pulse and blood pressure rise. Vomiting and diarrhea are frequent. As the withdrawal syndrome increases, the patient becomes restless, pessimistic, surly, and irritable and exhibits an unpleasant increased psychomotor activity. Considerable prostration may occur.

The multiplicity of suggested therapies for the narcotic withdrawal syndrome suggests the relative inadequacy of present methods of treatment, none of which is able to completely suppress the symptoms of this often protracted and stormy syndrome. Usually withdrawal involves the gradual reduction of dosage with a substitution for the habitual opiate of a similar but more innocuous drug, usually Methodone. Disadvantages of such treatment are its length, its inability to entirely suppress the withdrawal syndrome, and often the failure of the patient to complete the treatment because of the discomfort he suffers.

Shock Therapy

Various types of shock therapy have been suggested from time to time as methods of treatment for the narcotic-withdrawal syndrome. Such agents as Metrazol,[1] 70% carbon-dioxide inhalation,[1] nonconvulsive faradic shock,[2] and insulin-induced hypoglycemia[3,4] have been tried with only partial success. Electroshock therapy has been noted by

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Kalinowsky[5,6] and Gallinek[7] to have been successful in alleviating the symptoms of the narcotic-withdrawal syndrome. In 1953 Thigpen and Cleckley[8,9] reported a series of 35 narcotic addicts in whom the narcotic-withdrawal syndrome had been completely eliminated by the use of electroshock therapy. Since that time there have been no further reports on the use of this potentially promising method. The following case report demonstrates its effectiveness.

Case Report

This was the first admission* of a 32-year-old white male Demerol addict admitted from the city jail where he was being held on a felony charge. The patient had been taking Demerol for one year prior to admission. The initial dose had been 50 mg. intravenously twice daily, to alleviate his despondent feelings following the suicidal death of his divorced wife; since then he had been on doses as high as 1,200 to 1,500 mg. per day. Five months prior to admission he was gradually able to reduce the dosage to 400 mg. per day and shortly thereafter discontinued the drug, developing severe nausea, vomiting, "fear," headache, sweating, restlessness, and cough. The patient then resumed the self administration of Demerol but made a second attempt at withdrawal four months prior to admission, taking over a period of one week Thorazine, Compazine, and meprobamate, all without relief of withdrawal symptoms. Then he again resumed Demerol and attempted to continue on the dose which kept him just short of withdrawal symptoms, usually 300 to 500 mg. per day. He had taken morphine on only two occasions in the year prior to admission and gave no history of significant barbiturate ingestion.

Educational Background

The patient had completed school through the seventh grade and worked at various laboring jobs until age 24 when he completed two out of three years of a nurses' training course. This training plus the additional experience which he received in various prison hospitals where he had been incarcerated in the ensuing six years enabled him to secure employment as a surgical aide in a general hospital one and one half years prior to admission. There, through an elaborate system of double bookkeeping, the patient began taking Demerol. He had had one previous psychiatric hospitalization five years prior to admission, following a suicide attempt in which he "slashed the left antecubital fossa" following an argument with his wife.

Initial physical examination demonstrated a slender, apprehensive, tremulous white male who exhibited occasional retching, mydriasis, and numerous venapuncture marks in the right antecubital fossa, both forearms, and the backs of both hands.

Mental Status

Mental status examination demonstrated major concern on the patient's part regarding the early withdrawal symptoms which he was experiencing; he voiced considerable anxiety over the possibility of "cold turkey" withdrawal from Demerol. He appeared to be of above average intelligence and used many medical terms correctly. The remainder of the formal mental status examination was unremarkable

Laboratory Data

The following initial laboratory data were obtained: Wasserman negative; hematology: hemoglobin 15.4 gm.%, leucocytes 5200 with a normal differential; urinalysis: sp. gr. 1.024, pH 5.0; albumin, sugar and microscopic negative; blood chemistry: fasting blood sugar 88 mg.%, CO_2 25 mg.%, Cl 98.5 mEq/L, Na 141 mEq/L, K 3.4 mEq/L and BUN 13 mg.%. A chest X ray was negative. Spine films and electrocardiogram taken 15 days after admission were normal.

Minnesota Multiphasic

The patient's Minnesota Multiphasic Personality Inventory code type was 5″4′*36*2-1798/0′, a type most frequently associated with character disorders in which the patients are usually rather hostile and have a strong impulse toward socially-disapproved behavior. Such patients are frequently socially perceptive and verbally fluent and are more likely to express their aggression and hostility through well planned social manipulation than through direct physical aggression. They are usually "inner directed" and sensitive and show considerable self concern; they are frequently ambitious, clever, individualistic and place high value on cognitive pursuits and aesthetic interests.

Withdrawal Treatment

The patient was placed on Demerol 50 mg. intramuscularly every two hours on admission. This dose just averted the appearance of a major withdrawal syndrome, although for the following 17 days on this regimen the patient exhibited periodic nausea, restlessness, tremor, diaphoresis, muscular weakness and pain, diarrhea, headache, and vomiting. It became apparent that he was becoming tolerant to 600 mg. of Demerol a day and that this dose would no longer be sufficient to avert a major withdrawal reaction.

The withdrawal procedure was initiated 17 days after admission. Demerol was withdrawn over a four-day period in daily decreasing doses from 100 mg. every four hours to 50 mg. every four hours to 25 mg. every six hours to 50 mg. at bedtime.

Electroshock Treatment

Concomitant with the withdrawal of the drug, the patient was given a daily electroshock treatment using sodium pentathol, 125 mg. intravenously for sedation, and Anectine, 15 mg. intravenously for muscular relaxation. These were continued for three days after complete withdrawal for a total of seven electroshock therapy treatments. During the withdrawal period the patient experienced no objective or subjective withdrawal symptoms. On the third day he attempted to refuse two doses of Demerol. A planned program of supportive therapy consisting of sedation and medication for possible nausea, vomiting, diarrhea, headache, anorexia, and muscular pain proved to be unnecessary. During the withdrawal period vital signs were followed closely and remained stable. The patient was weighed daily and gained nine pounds. With the exception of the usual postelectroshock therapy treatment confusion which cleared rapidly, he remained completely asymptomatic in the ensuing period and two weeks after withdrawal was discharged to stand trial.

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*To Hennepin County General Hospital.

Discussion

This case illustrates the effectiveness of electroshock therapy in completely suppressing the narcotic-withdrawal syndrome and corroborates the findings of Thigpen and Cleckley. The patient served as his own control. The findings by history of withdrawal symptoms on two occasions when the patient attempted to withdraw drugs, the presence of objective and subjective symptoms of withdrawal on admission and during the subsequent hospitalization, with the development of tolerance to a maintenance dose, indicate that the patient would have suffered a severe withdrawal syndrome without treatment.

Several explanations have been offered for the effectiveness of this method. Gallinek[7] suggests that in narcotic addiction electroshock therapy is effective in breaking up a learned behavior pattern, and Thipgen and Cleckley[8,9] suggest that the confusion caused by the treatment seems highly desirable. Along these lines the findings of Faltz and Lowell[10] are of interest. They demonstrated the efficacy of either stereotaxic cingulumotomy, resection of the cingulate gyrus, or frontal lobectomy in suppressing the narcotic-withdrawal syndrome in experimentally addicted monkeys. In their series lobectomy appeared to be the superior method. They postulated that the cingulum was an association fasiculus from the frontal lobe to the limbic system and that the autonomic hyperactivity of the narcotic-withdrawal syndrome was modified by cingulumotomy through loss of emotional facilitation of the limbic system from the frontal lobes. It is possible that what is produced by electroshock therapy is in effect a temporary functional lobectomy in which facilitation of the limbic system is absent by virtue of the altered function of the frontal lobe. The autonomic hyperactivity of the narcotic-withdrawal syndrome is thus averted.

Conclusions

1. Electroshock therapy is a useful method of treatment for complete suppression of the narcotic-withdrawal syndrome.

2. Further clinical investigation of this method is required and this case is presented with the hope that similar cases may be treated by this method and reported.

3. Temporary functional lobectomy is hypothesized as the mechanism by which electroshock therapy suppresses the narcotic-withdrawal syndrome.

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The truth doesn't hurt unless it ought to.—Forbes Epigrams

Pregnancy

with

Dermoid Cyst

Case of Intrauterine and Extrauterine

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TABLE I.

CASE	EXTENT OF PREG. AT OPERATION	PREOP. DIAG.	TYPE & LOC. OF CYST	LOC. OF ECTOPIC PREG.	POSTOP. DIAG.	OUTCOME
5 Daleas	$2\frac{1}{2}$ mo.	Torsion of rt. ovarian cyst	Rt. ovary loc. not stated	Rt. tube	Torsion of cyst with rupture of tubal preg., rt. side. Uterine preg.	Spont. abortion of uterine fetus
6 Ramos & Wernicke	3 mo.	Left tubal preg.	Left ovary dermoid	Left tube	Tubal preg. with dermoid cyst, left side. Uterine preg.	Spont. abortion of uterine fetus
7 Adams, Leckie & Murdoch	8 wks.	Torsion of rt. ovarian cyst; uterine preg.	Rt. pseudomucinous adenoma	Left tube	Rt. ovarian cyst, no torsion, left tubal preg. Uterine preg.	Spont. delivery at term
Reinhardt	$2\frac{1}{2}$-3 mo.	Ovarian cyst, uterine preg.	Rt. ovary dermoid	Rt. tube	Rt. dermoid cyst, rt. tubal preg. Uterine preg.	Spont. delivery at term

CONCURRENT ECTOPIC and intrauterine pregnancy is an infrequent clinical entity, the incidence of which has been estimated at from one in 12,000 to one in 30,000.[1] This condition has been widely reported in medical literature. Ovarian tumors complicating pregnancy have also been fully reported, the incidence quoted varying from one in 102 pregnancies to one in 8,000. It is therefore assumed that these conditions are not rare. However, the simultaneous existence of all three would seem to be exceedingly rare. Adams, Leckie and Murdoch[2] could find reference to only two previous cases in the last forty years. As further search has revealed no other reports, the case described here is the fourth.

The diagnostic problems involved and the timing of treatment or surgical intervention present such hazards that unsuccessful cases are either unrecognized or unreported; therefore the condition may not be as rare as the dearth of literature indicates.

Case Report

A white farmer's wife was admitted to the hospital on 9-15-61 complaining of severe pain in the right lower abdomen, nausea and vomiting. Menstrual history revealed a probable normal period in May, none in June, and slight bloody spotting for two or three days in July, August, and September. She had undergone two curettages following miscarriages; otherwise her history was negative.

Uterine Pregnancy and Ovarian Mass

Physical and laboratory findings were normal except for pallor of the skin and conjunctiva and a low hemoglobin of 10.8%. A round, firm, very tender mass was palpable in the right lower quadrant. Pelvic examination revealed a globular mass in the right adnexa approximately 15 cm. in diameter. The uterus was enlarged two and one half times normal size. A frog test was negative, but a gonad hormone test with serum was positive.

The patient was given one unit of blood, bringing the hemoglobin to 12.9 gr. %. Ectopic pregnancy was suspected; however, the patient became asymptomatic and, with the frog test positive and the uterus enlarged, she was discharged on 9-22-61 with the warning to report immediately any recurrence of symptoms. The discharge diagnosis was uterine pregnancy with ovarian cyst.

Operative Findings

One week later the patient was admitted to the hospital, and again the presenting symptoms were lower abdominal pain, nausea and vomiting. The uterus was enlarged to a two-and-a-half to three months pregnancy, with a palpable mass adherent to the uterus in the right adnexa. Laboratory findings, however, were within normal limits. On 9-30-61 the patient was brought to surgery for an exploratory laparotomy. The preoperative diagnosis was ovarian cyst complicating uterine pregnancy. At surgery the right ovary was found to be greatly enlarged and cystic in appearance, one portion of the mass containing chocolate-and-blood-like fluid. A right salpingo-oöphorectomy was done.

Pathologic Findings

The pathology report stated that the tissue consisted of the right tube and ovary, which weighed 175 grams. It was bilobate, one lobe representing a tube, the other an ovarian cyst. The cystic lobe was eight cm. in diameter, the interior made up of about six locules, two of these filled with clear mucus, the remainder with hair and sebaceous material. Between the locules was a slender irregular bar of bone. The other lobule proved to be a cystic space filled with old blood clots, with a fibrous wall from one to three mm. in thickness. From its position it resembled a Fallopian tube dilated with blood. Microscopic examination revealed that the tissue surrounding the hemorrhagic mass was made up of remnants of a dilated tube, the hemorrhagic mass itself containing many chorionic villi. Sections of the ovarian cyst showed glandular tissue resembling salivary glands, fat, muscle, cartilage, nerve and skin structures. The final pathological diagnosis was ectopic pregnancy of Fallopian tube and dermoid cyst of the ovary.

The patient's surgery was well tolerated and she was discharged on 10-7-61, after which she was followed regularly during the course of her uterine pregnancy. On April 24, 1962, she delivered, spontaneously, a full-term living girl.

Comments

According to Schaefer,[3] combined uterine and extrauterine pregnancy is seldom correctly diagnosed before surgery. It is his opinion that a diagnosis of combined pregnancy should be considered in every patient who presents unusual symptoms early in pregnancy, such as:

1. A history of previous ectopic pregnancy.
2. Unilateral lower abdominal pain with signs of uterine pregnancy.
3. Severe nausea and vomiting in a patient thought to have an ectopic pregnancy.
4. Vaginal bleeding with signs of peritoneal irritation.
5. Palpation of a tender adnexal mass in the presence of an enlarged uterus.

According to Fleisher and Seaman,[1] intrauterine fetal survival rate in association with heterotopic pregnancy is about 54%.

The symptoms of ectopic pregnancy and

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*Our Lady of Mercy Hospital.

troublesome ovarian cyst may be markedly similar: disturbed menstrual function, abrupt and intense abdominal pain, vomiting, marked faintness or collapse.

Chowdhury,[4] in an analysis of 24 cases of pregnancy complicated by ovarian cyst, found one third of the cases incorrectly diagnosed before surgery, with ectopic pregnancy being the commonest error in the first trimester. Of the 24 cysts, 14 were dermoids.

The following table comparing the known cases of intrauterine and extrauterine pregnancies complicated by ovarian cysts illustrates the variety of conditions and diagnostic problems.

It may be of interest to note that in the two cases where the ectopic pregnancy had not ruptured, the intrauterine fetus was saved. With only four cases no significance can be attached; but as shock associated with rupture is a factor, the surgeon confronted with an emergency may fail to exercise the same caution that a more deliberate operative procedure allows. Careful instrumentation, delicacy in palpation of the uterus, and awareness of the possibility of more than one pregnancy may prevent damage to the fetus and possible abortion. Whether the emergency is caused by an ovarian cyst, an ectopic pregnancy, or both, the same concern for an intrauterine fetus should be exercised.

If abortion of the intrauterine fetus should occur first, there is the possibility that an ectopic pregnancy may be missed, which could then progress to rupture. If the symptoms listed by Schaefer persist following abortion, the indications for exploratory surgery are clear.

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IT'S THE LAW

Failure of Physician to Follow Directions

Failure of a physician to follow directions issued by a drug manufacturer for the administration of its product constituted intervening negligence which relieved the manufacturer from liability under an implied warranty.

The appellate court held that the intervening negligence of the physician precluded application of a warranty. It ruled that warning given to physicians was adequate and that a warning to the public was not required. It also said that a drug manufacturer's implied warranty does not run to those who happen to be allergic to the drug unless the allergy is one possessed by a substantial number of the possible users. The manufacturer's duty is to reasonably guard against probabilities, not mere possibilities, the court said.

Magee v. Wyeth Laboratories, Inc., 29 Cal. Rptr. 322 (Cal., March 22, 1963)

Take Time Every Day

Take Time TO READ — It is the fountain of wisdom.

The Paraplegic Patient

Long-Term Care

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CHRONIC CARE of the spinal-cord-injured patient is as important a responsibility and, in some instances, presents as many critical problems as the care of the recently injured patient. Neglect or inadequate treatment will cause the death of the paraplegic patient just as surely as if the physician ignored the acute problems following the initial injury. When death or morbidity occurs during the chronic phase of the disease, it is often accepted as inevitable rather than as a consequence of improper care.

A dramatic historical example of neglect in caring for a paraplegic patient can be found in the case of a president of the United States. "On July 2, 1881, President Garfield was shot by a disappointed office seeker. He was attended by the Surgeon-General of the U.S.A. and other eminent medical persons. Although his legs were paralyzed and he complained of pain and heaviness in his legs and lost control of bladder and bowel, the nature of his injury was not recognized until after death. He died on September 19, 1881. Autopsy revealed the bullet had traversed the first lumbar vertebra causing paralysis. The patient's downhill course during the summer was typical of a spinal cord injury, for he experienced fever, chills, weight loss, and infected pressure sores. The final cause of death was rupture of a traumatic aneurysm on the splenic artery."[1]

The Acute Problem

The care of the spinal-cord-injured patient is fortunately vastly improved over the care in President Garfield"s time. In fact, there has been a marked improvement between world wars. In World War I only 20% of those incurring spinal cord injuries reached the U. S. and only 10% of these lived longer than one year. During World War II 80% survived to return from the battle front.[2]

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*Director, Rehabilitation Services, Kenny Rehabilitation Institute.

At the present time it is exceedingly rare for a patient to die from the acute effect of spinal cord injury; with good care the lifetime mortality of the paraplegic should not differ much from that of the general population. Breithaupt and others[3] reported a mortality of 15.7% in spinal-cord-injured patients treated between 1945 and 1958; Guttmann[4] followed 1000 cases in England between 1944 and 1954, listing a mortality rate of 8.3%; the Veteran's Administration office in Washington described a mortality of 15% for paraplegic patients treated between 1946 and 1955. These figures are probably lower than the death rate for the total paraplegic population, as they come from spinal-cord-injury centers where sophisticated follow-up care is possible. The isolated practitioner is in a difficult situation; he does not see enough spinal-cord-injured patients to learn of their special needs.

Paraplegia is rapidly becoming a problem of the private physician because of an enlarging population not eligible for veterans administration care. Comprehensive rehabilitation centers, such as the Kenny Rehabilitation Institute, are seeing a greater number of these patients each year, all of whom will be returning to the private practitioner for long-term care. Because of rehabilitation, the paraplegic patient has reached a high degree of functional independence and is psychologically ready to once again take his place in the community. It is the responsibility of the private practitioner to keep him there.

The Spinal Man

Transection of the spinal cord causes physical and physiological alterations that can produce an unusual array of problems completely foreign to normal man. Besides the obvious spastic paralysis, the paraplegic patient may have mass flexor and extensor spasms of the legs and trunk. There is a loss of all sensation below the level of the lesion, but despite the absent sensation some patients have intractable pain. Normal control of the bladder and bowel is lost and sexual function is interfered with. With spinal lesions above the fifth dorsal vertebra dysfunction of the autonomic nervous system causes lability of the blood pressure, impaired temperature regulation and syncopy with exertion.

Genitourinary Disease

Autopsy studies have indicated that renal disease is the leading cause of death in paraplegics. Deittrick and Russi[5] place renal disease as the primary cause of death in 20% of 55 paraplegics studied; Breithaupt et al.[3] stated that renal failure was the cause of death in 42.5% of 94 paraplegics. Furthermore, both Dietrick and Breithaupt found disease in the genitourinary tract in nearly all persons studied.

The abnormality most responsible for renal morbidity is ureterovesical reflux. Incompetence at the ureterovesical junction allows infected urine from the contracting bladder to be pushed in a retrograde fashion to the kidney. Pyelonephritis results with associated high fever and shaking chills.

Unfortunately this condition is often misdiagnosed as cystitis; hence the physician fails to appreciate the damaging renal effects of repeated bouts of pyelonephritis and the later developing hydronephrosis. If the ureterovesical reflux is recognized, the treatment is simple and effective. The likelihood of reflux is lessened if the bladder is kept empty by straight catheter drainage. Several operative procedures are of value in selected cases, but their description is beyond the scope of this paper.

Loss of Sensation

Pain is necessary to prevent man from abusing his skin and joints; it is also a warning signal of intra-abdominal disease. Deittrick[5] reports acute abdominal catastrophes as the cause of death in 10% of his cases. Breithaupt[3] used the broader category "gastrointestinal disease," and listed it as the cause of death in 50% of the 40 cases he autopsied; however, in the discussion of specific gastrointestinal diseases, such conditions as perforated ulcers, ruptured appendices, and acute dilatation of the stomach, were described.

The physician caring for the paraplegic must be alert to his altered reaction to intra-abdominal disease. With sensory loss below the sixth dorsal vertebra there will be no peritoneal sensation and with lesions of the fourth dorsal or higher vertebra, sensation in the viscera will also be lost. The physician should be aware of such autonomic clues as sweating, flushing of the face and neck, obstruction of nasal airways, nausea, dilatation of the pupils, and bradycardia as a warning of abnormal activity in the intra-abdominal viscera.

Decubital Ulcers

Pressure sores are another serious consequence of missing pain sensation. When a pressure sore exists, continued weight-bearing will lead to deeper and deeper necrosis and chronic infection. Breithaupt[3] listed infected pressure sores as the cause of death in 7.4% of his cases, while Deittrick[5] said generalized infection, a consequence of chronically infected pressure sores, caused the death of 99% in his study. The physician must understand and impress upon his patient the role of pressure in the etiology of these sores and he must constantly remind him that only by freeing the affected areas of weight-bearing can healing occur.

Autonomic Dysfunction

In lesions about the fifth dorsal vertebra the sympathetic nervous system is isolated from its control centers, resulting in vasomotor instability. With the assumption of a sitting or standing posture severe hypotension and syncopy can occur, due to pooling of blood in the splanohnic vessels and in the large veins of the legs. Abdominal and leg compression from corsets, binders, and leg wrappings will help correct this situation.

Frequently an autonomic dysreflexia occurs with serious elevation of blood pressure from distension of the bladder or anal canal. Systolic blood pressures approaching 300 mm. of mercury may result, and in susceptible individuals there is a real danger of intracerebral hemorrhage. Treatment consists of avoidance of bladder distention by keeping the patient on straight catheter drainage. Parasympatholytic drugs such as Banthine are of value; occasionally ganglionic blocking agents must be used. In intractable cases the reflex arc initiating the severe vasoconstriction must be abolished by the subarachnoid injection of absolute alcohol in the region of the conus.

Respiratory Impairment

Transection of the cervical cord leaves only the diaphragm to perform respiration. Vital capacity is not greatly reduced, but the loss of intercostal and abdominal muscles seriously impairs the coughing ability of the paraplegic patient. As a result the physician must observe the patient closely during upper respiratory infections for signs of inadequate clearing of secretions from the lungs. Abdominal support from either a binder or a corset or by manual compression aids in producing a more effective cough.

Pain

Pain is most common in patients with cauda equina lesions; the incidence reported by various authors[2] ranges from 5% to 50%. The pain noted in spinal-cord-injured patients below the level of their lesion is of two types. It may be a radicular pain, noted at or slightly below the level of the lesion, and is probably due to irritation of the nerve roots at or near the fracture site. It is readily amenable to the usual techniques of handling radicular pain such as the injection of anesthetic agents. The second and more difficult pain to treat is the vague, poorly localized, burning sensation which is probably of sympathetic origin, similar to the phantom limb pain of the amputee. The best treatment is to divert the patient's attention from the pain while reassuring him that it will gradually disappear. The patient soon learns to live with these abnormal sensations and no longer interprets them as pain.

Conclusions

The physician caring for the spinal-cord-injured patient must remember that he is dealing with a "spinal man" whose responses to external stimuli are altered and who has special medical problems. With sophisticated care the paraplegic's life expectancy should not differ much from the normal man's. Neglect or improper care will most surely lead to the patient's early demise.

Special problems include progressive loss of renal function due to pyelonephritis aggravated by ureteral vesicle reflux. Loss of sensation leads to pressure sores and makes diagnosis of acute abdominal problems difficult. Imbalance of the autonomic nervous system causes unusual problems such as hypotension, syncope, severe transient hypertension, and poor temperature control. Cough in the paraplegic is greatly impaired. Finally, intractable pain may exist with the ever present danger of addiction.

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*Mother's Day—May 10**

God can't be always everywhere: and so invented mothers—Sir Edwin Arnold

To Mama

A Mother's Day Poem by a Teen Age Girl

Without you I have nothing.
The pink blossom of spring is gray and withered—
The dew of morning is cold, crushing the grass beneath—
The fragile dove of night sings of joy no longer.
But with you the earth is mine.
The clouds, the trees, the birds, the flowers radiate of light
And the light moves forward; beyond the hill and across the sea,
And carries with it happiness, for light is love.
I breathe of air so fresh, so pure;
I see a clearing in a forest of twine.
White violets; pink ferns; a cloud of gold;
I hear the clashing of waves — the breeze that cools the earth
You give me strength.

—Sarjae

If you would reform the world from its errors and vices, begin by enlisting the mothers.—C. Simmons

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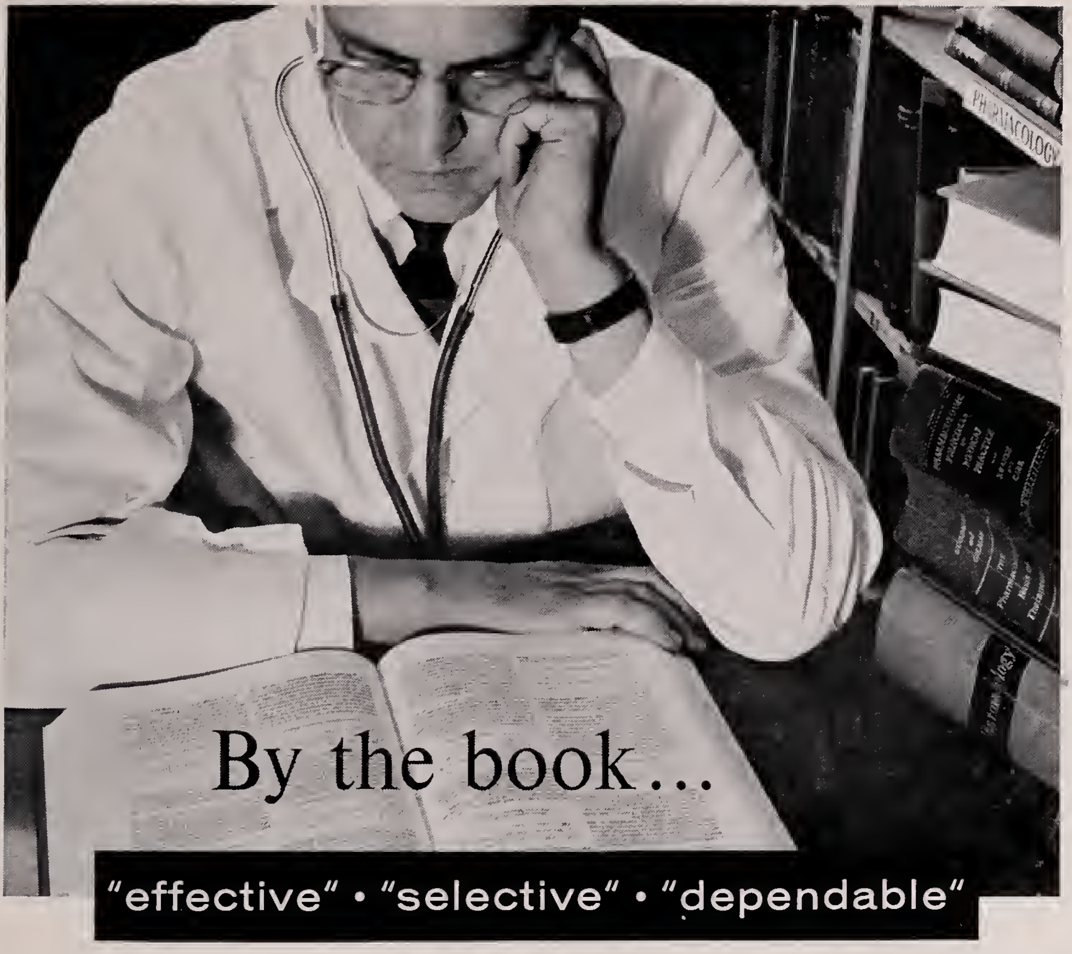
*See page 510 Dr. Lester's Mother.



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Side effects: Although there has been no evidence of tolerance, withdrawal symptoms or excessive self-medication, 'Soma' Compound and 'Soma' Compound with Codeine, like other central nervous system depressants, should be used with caution in addiction-prone individuals. While codeine addiction is relatively rare and easily broken, the same precautions must be observed as for any other opium alkaloid. Nausea, vomiting, constipation and miosis are possible codeine side effects. Should symptoms of hypersensitivity occur, discontinue medication.

Contraindications: None reported.

Complete product information available in the product package, and to physicians upon request.

Dosage: Usual dosage is 1 or 2 tablets 4 times daily.

Supplied: 'Soma' Compound is available in orange, scored tablets; bottles of 50. 'Soma' Compound with Codeine (narcotic order form required) is available in white, lozenge-shaped tablets; bottles of 50.

CSO-1054

Editorials

The Fifty Year Club

AT THE annual meeting of the Minnesota State Medical Association in Rochester this month those members completing fifty years of medical practice will be honored. Fifty years of medical practice should be celebrated like a golden wedding. As every successful practitioner of medicine knows, the doctor is wedded to his practice and the fifty year mark deserves special recognition. Thirteen members will receive their fifty year service pins this month. Each of these hung up his shingle in 1914 or thereabouts. We seize the opportunity to republish some medical extracts of articles printed at that time.

The following quotations are illustrative of medical thought of fifty years ago.

J. A. Macwilliam (Aberdeen, Scotland) (Heart): "The auscultatory method of estimating blood pressure, proposed by Korotkov of St. Petersberg in 1905, has received comparatively little attention in this country — much less in Germany." (At this time systolic blood pressure was usually estimated by the palpatory method; the diastolic method by estimating visually the point of maximum excursion of the mercury column. ED.)

James E. Moore (Minneapolis) (J.A.M.A.): "The time to decide whether a case of appendicitis is catarrhal, perforative, or gangrenous is after the surgeon has removed the specimen. . . . With operation at the present time the mortality rate is near 5% and in hospitals under expert surgeons it is even less than this."

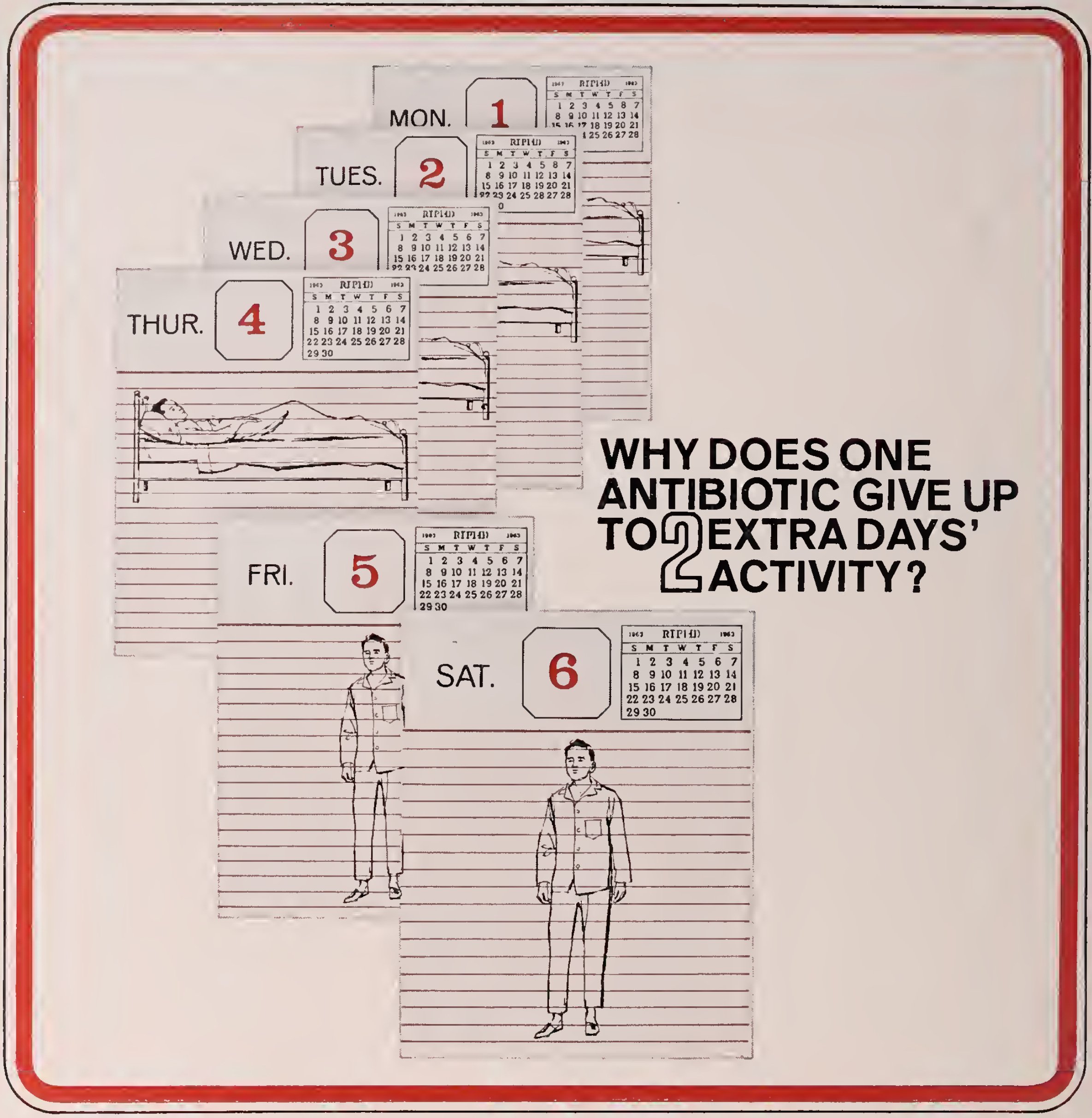
University of Minnesota Medical School (J.A.M.A.): University of Minnesota Medical School, E. T. Lyon, dean. Total registration for 1913, 169; graduates 30. Tuition — $150 each year.

Editorial J.A.M.A. (Anon.) "We may well admit that carbohydrate metabolism in the body is in some way bound up with the function of the pancreas without being able to give a final verdict whether the acinous tissue or the islands of Langerhans are the most important epithelial elements concerned in this role of the gland."

Charles W. Burr (Philadelphia) (Trans. Am. Med. Psychol. Assoc.): "I remember an old and distinguished professor of medicine in Germany who, when some years ago I told him I had aspirations to become a neurologist and alienist, looked at me kindly and a little quizzically, and then said: 'Be careful, my young friend, alienists are all a little queer.' "

Russell D. Carmen (Rochester): "I have heard clinicians remark that the Roentgen ray is of considerable help in carcinoma of the stomach but of little aid in ulcer. . . . The rarity of Roentgenologic findings (in diverti-

Continued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culitis of the large bowel) can be understood from the fact that only one case has hitherto been reported."

William J. Mayo: "Gastrojejunostomy is the most generally useful operation for gastric ulcer. . . . Within one hundred years we have seen the leadership of medical science pass from England to France, from France to Germany. Modesty prevents me from naming the country to which it will go next. . . . New forms of taxation are now being devised, not for the protection of property, which was the basis of original taxation; but a tax on property for the protection and betterment of the individual. Of these the income tax is the entering wedge."

The following items are taken from the St. Paul Medical Journal Volume 16 (1914).

B. T. Green (Brookings, S. D.): "There is much to discourage the man in general practice. This is particularly true in the field of surgery where he has on the one hand the bid of the specialist and on the other the well grounded belief of his lay patron that only the specialist can be trusted with his surgical ills."

Arthur Hirschfelder (Prof. of Pharmacology, Univ. of Minn.): "In the every day use of drugs we have passed through various stages from the days of Sydenham who was ranked with the mild prescribers when he placed only eighteen drugs in one prescription to the later days of Skoda who gave nothing at all or at most a placebo. That a little of this unfortunately remains is indicated in the tendency to say of a medical man 'He is a fine diagnostician' and not 'He treats his patients well.' "

Editorial — Whole Time Teachers of Medicin (anon.): "An opportunity is created by this endowment (Rockefeller) to inaugurate a great reform in the teaching of medicine and Johns Hopkins is to be congratulated on having been selected for this purpose. The clinical professors appointed, probably Barker in Medicine, Halsted in Surgery, and Howland in Pediatrics, will covenant to give their entire time to teaching, to the work of the medical school, and to accept for themselves no fees from private patients."

Miss Eleanor J. Hamilton (RN) (Minneapolis): "In our hospital I give anesthetics for something like thirty-five different surgeons, and without going further into detail it will be obvious that sometimes I anesthetize the surgeon rather than the patient. That is to say, I have to give more consideration to the surgeon than to the patient."

Editorial — The American College of Surgery (anon.): "At present time we believe that only a very small majority of those who have been elected to fellowship in the College from Minnesota confine their work to surgery. Most of them take all they can get of general practice; and while without exception the men to whom we allude are able surgeons, we cannot help feeling they would be better surgeons if they should announce that hereafter they would not engage in general practice, and stick to it."

C T. Granger (Rochester). Trichiniasis: "It is not practical (muscle biopsy), textbooks to the contrary notwithstanding, to harpoon sufficient tissue to make a satisfactory examination."

Reports and announcements of Society meetings: The Third Midsummer Meeting of the Southern Minnesota Medical Association at Winona, August 20 and 21. . . . "After a very enjoyable luncheon which was served at the Arlington Club, the association assembled on the elegant pleasure steamer Oronoco, by the courtesy of Drs. W. J. and C. H. Mayo, and were given a most enjoyable excursion on the river. During the excursion the balance of the program was taken up and the work of the Association was completed."

J. W. Andrews (Mankato). Intracapsular Fracture of the Femur: "The best and most modern method of diagnosing fracture is by means of the X ray, but this is available only in exceptional cases in the fracture under consideration. The ordinary portable machine is not reliable for deep work and the larger and better machines are generally in the physician's office where it is quite impractical to move the patient. We must depend therefore upon the signs and symptoms to make our diagnosis."

George Earl (St. Paul). Thrombosis and Lung Embolism: "As to the frequency of this condition, it is doubtful it is appreciated. . . . The extreme cases are usually diagnosed, but

Continued

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the more moderate masquerade under the head of pleurisy, postoperative pneumonia, etc., not but that such conditions do occur, although postmortems would demonstrate in a large percentage of cases thrombosis and embolism."

Editorial — The Destruction of Louvain and ts University. (Anon):

"The wanton destruction by the Germans of the University and the Library of Louvain may be instanced as an absolutely irreparable loss to the whole world. It was at Louvain that Andreas Vesalius first studied and later became one of its most eminent professors, and it was through him that Louvain became the most important anatomical center in the world. Vesalius was born in Brussels in 1514. This very year it had been arranged that an official celebration of the four hundredth anniversary of his birth should be held in Brussels in December next."

Reuben Berman, M.D.
Minneapolis, Minn.

Drug Addiction

THE PROBLEM of drug addiction has been a matter of serious concern to all physicians, inasmuch as it has been widely considered an occupational hazard to our profession. Many a promising or established career has been destroyed or thwarted as a result of addiction. On the other hand, a successful rehabilitation of a doctor whose emotional illness has manifested itself in symptoms of addiction has been extremely gratifying, both from the standpoint of re-establishing harmony in the family as well as a return to contributing effectively to society professionally.

The causes of addiction have remained obscure, although much has been written on the subject. It appears that two types of persons are vulnerable: (1) the addictive personality; and (2) the depressed person. What constitutes the "addictive personality" is still controversial. Suffice it to say that it includes people with all kinds of addictive problems, such as alcohol, sedative drugs, tranquilizers, narcotics, and perhaps nicotine dependence. The Alcoholics Anonymous movement, which has been so successful in rehabilitating people with alcohol addiction, claims that omnipotent traits in the personality of alcoholics play an important role. Others believe that deep-seated personality disorders or character defects predispose a person to reliance on continued self-medication. Low frustration tolerance to life's stresses and oral fixations have also been accused of being etiologic in the development of alcohol addiction. Many experienced observers and workers in this field are impressed with similar characteristics found in patients with the problem of drug dependence. For these it is believed that treatment based on the principles of A.A. is most helpful.

In the second group the addiction is thought to be precipitated by an acute traumatic event in a person of previously stable and mature personality structure. Such a traumatic event could be a death of an important family member, an accident resulting in death or severe invalidism, a suicide of a spouse or child, etc. Any major event producing guilt which is unresolved is apt to cause an episode of severe depression, which the involved person attempts to handle by himself with self-medication leading to drug dependence and fairly rapid addiction. This type of addiction has an excellent prognosis, if adequately treated with intensive psychotherapy, or in some cases with electroshock therapy.

The method of withdrawal has been no real problem to the expert for any of the addictions. Although many different techniques have been described — substitution therapy, gradual or abrupt "cold turkey" withdrawal, electroshock (see page 525), steroids, glycyrrhiza, ataractic medication,

Continued

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etc. — any method can be successful in experienced hands, with full knowledge of withdrawal symptoms and complications. Success or failure with addictive problems does not appear to be based on the method of withdrawal chosen, but on intensive follow-up treatment — the principal mode of therapy. It is in this area where the high rate of relapses seems to be determined. Much further research needs to be done in the field of addiction, which presents such an immense social problem and a special hazard for the medical profession.

Werner Simon, M.D.
Minneapolis, Minn.

Urologic Problems in Paraplegia

The chronic paraplegic population is increasing as a result of the increase in serious accidents and of improved medical care during the acute phase of the illness. Several large medical centers in the United States are devoted exclusively to the treatment of these individuals. Facilities for the chronic care of the "spinal man" are so overburdened that the patients must eventually be returned to physicians in their communities. Elsewhere in this issue of Minnesota Medicine Dr. Schoening has discussed the chronic care of the "spinal man." The family physician is not adequately trained to deal with the many problems peculiar to these patients without the help of a team of specialists.

Kidney disease is still the commonest cause of death; it consists of pyelonephritis, hydronephrosis, renal calculi, and ureterovesical reflux. Operations to correct the latter are neither simple nor consistently successful; catheter drainage neither prevents its occurrence nor abolishes it. A compensated bladder may decompensate at any time; the residual urine should be measured frequently, urine culture obtained, and the status of the upper urinary tract determined by excretory urography. Occasionally a cystogram for reflux is indicated.

Autonomic nervous system dysreflexia, fortunately not too frequent, can prove to be very troublesome and may not respond to any medication. Renal function tests are of considerable value. Despite normal appearing excretory urograms, there may be impairment of renal function as measured by the glomerular filtration rate, renal blood flow, and renal tubular excretory and reabsorptive capacity. Urethritis, prostatitis, epididymitis, benign and malignant prostatic hypertrophy also occur. On occasion the neurological deficit may mask serious complications or deterioration of the urinary tract. The urological problem remains throughout the life of the paraplegic requiring perpetual care.

Milton P. Reiser, M.D.
Minneapolis, Minn.

Asthma in Children

The article by Dr. Strem in this issue (page 511) is a timely one, for allergic disease is one of the common and at times frustrating aspects of general or pediatric practice. Children having asthma constitute a small but significant segment in this practice. Asthma is the most serious of the commonly met allergic manifestations and at times may be life-threatening.

The frequent onset of the disease in early life needs constant re-emphasis, for some physicians still doubt that children under the age of three or four years can have asthma. It is likewise well to emphasize the special differential diagnosis which must be employed when dealing with infants and children as compared with that used when dealing with adults.

Opinions continue to differ regarding the more important etiologic agents in asthma of childhood. This writer must take issue with Dr. Strem and say that, in his experi-

Continued

most effective in the obese diabetic...

Recent reports suggest...insulin and sulfonylureas may accelerate lipogenesis,[1-5]...serum "insulin" levels are often elevated in obese diabetics[2,3,6]... DBI (phenformin HCl) reduces high blood sugars, lowers elevated "insulin" levels, tends to reduce body weight toward normal.[1,3,7-9]

In the obese diabetic (ketoacidosis-resistant), use of phenformin HCl together with a proper diet: **A.** acts to reduce high blood sugar without increasing fat synthesis or weight gain. **B.** does not increase already elevated endogenous insulin levels; may, indeed, act to restore more normal insulin levels. **C.** favors reduction of weight towards normal.

In the ketoacidosis-resistant obese diabetic not amenable to diet alone, hypoglycemic phenformin HCl appears to help avoid weight gain or reduce adiposity, factors which otherwise tend to make blood sugar control more difficult and to increase the likelihood of complications. However, in the ketoacidosis-prone diabetic, insulin is still the essential hypoglycemic agent.

Summary: Indicated in stable adult diabetes, sulfonylurea failures and unstable diabetes. Gastrointestinal side effects occurring more often at higher dosage levels abate promptly upon dosage reduction or temporary withdrawal. Occasionally an insulin-dependent patient will show "starvation" ketosis (acetonuria without hyperglycemia) which must be differentiated from "insulin-lack" ketosis, and treated accordingly. Use with caution in severe liver disease. Not recommended without insulin in acute complications (acidosis, coma, infections, gangrene, surgery). Consult product brochure for full information.

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ence and that of a number of others, inhalant and infectious factors are more important than foods. This seems to be true even in the first year of life.

For many years the term "emphysema" has been used to denote any condition which is manifested clinically by an increased anteroposterior diameter of the chest. However, this term is best reserved for the irreversible structural changes which occur in far-advanced pulmonary disease. It is better to refer to the situation more commonly encountered in those having poorly controlled or uncontrolled asthma as "hyperinflation" or "overinflation." This is more than a purely semantic argument, for it entails a better understanding of the actual situation. Most children with poorly controlled asthma have a hyperinflated chest. This can be demonstrated not only by the clinical appearance but also by the results of a pulmonary function test. It can be shown that if the asthma is brought under proper control, the pulmonary function test as well as the appearance of the chest will return to normal. True emphysema is not reversible in this fashion.

The number of drugs available for symptomatic treatment of the patient with asthma is limited. Such drugs are sympathomimetics, xanthines, expectorants, sedatives, and glucocorticoids. Although several drugs are available in each group, one may be more effective than another in a given patient, when used alone or in combination with other drugs. The reason for this is uncertain. It is most important that the general physician or pediatrician know one or two drugs in each group and be aware of their desirable and undesirable actions. It is how they are used and how much is administered that is highly important.

The pediatricians and generalists who treat children have a tremendous responsibility as they manage the child who has asthma, for there is good reason to believe that the better the patient is managed in childhood the less difficulty he will have as he grows older. Prophylaxis, particularly that relating to the use of soybean milk in infants from allergic families, makes theoretical sense, but is still an unproved procedure. There are several studies in progress throughout the country to learn the truth about this matter.

It has often been said, and Dr. Strem repeats the point, that children who have hay fever which is not properly treated — and particularly if treatment has been by hyposensitization — will later have asthma. There is some evidence refuting this belief and supporting the observation that some patients have mild hay fever and always will have mild hay fever. However, more evidence is needed in this regard.

Dr. Strem wisely points out that the prognosis in childhood asthma is still somewhat uncertain. Some textbooks, some articles, and some discussions with parents reveal more wishful thinking than fact when they talk about children outgrowing their asthma. More long-term studies are necessary. Studies in addition to those cited by Strem provide evidence, including 20 to 30-year follow-up, that approximately 50 per cent of the patients continue to experience wheezing. Not all of these persons have serious symptoms, but they do have some difficulty. One of the Danish studies has provided evidence that patients who seemed to have overcome their asthma after a 20-year follow-up subsequently had difficulty again.

Recognition of asthma in children, the proper management of children having this disease, and the counseling of parents of such children continue to constitute a challenge to all who are engaged in general or pediatric practice.

George B. Logan, M.D.
Rochester, Minnesota

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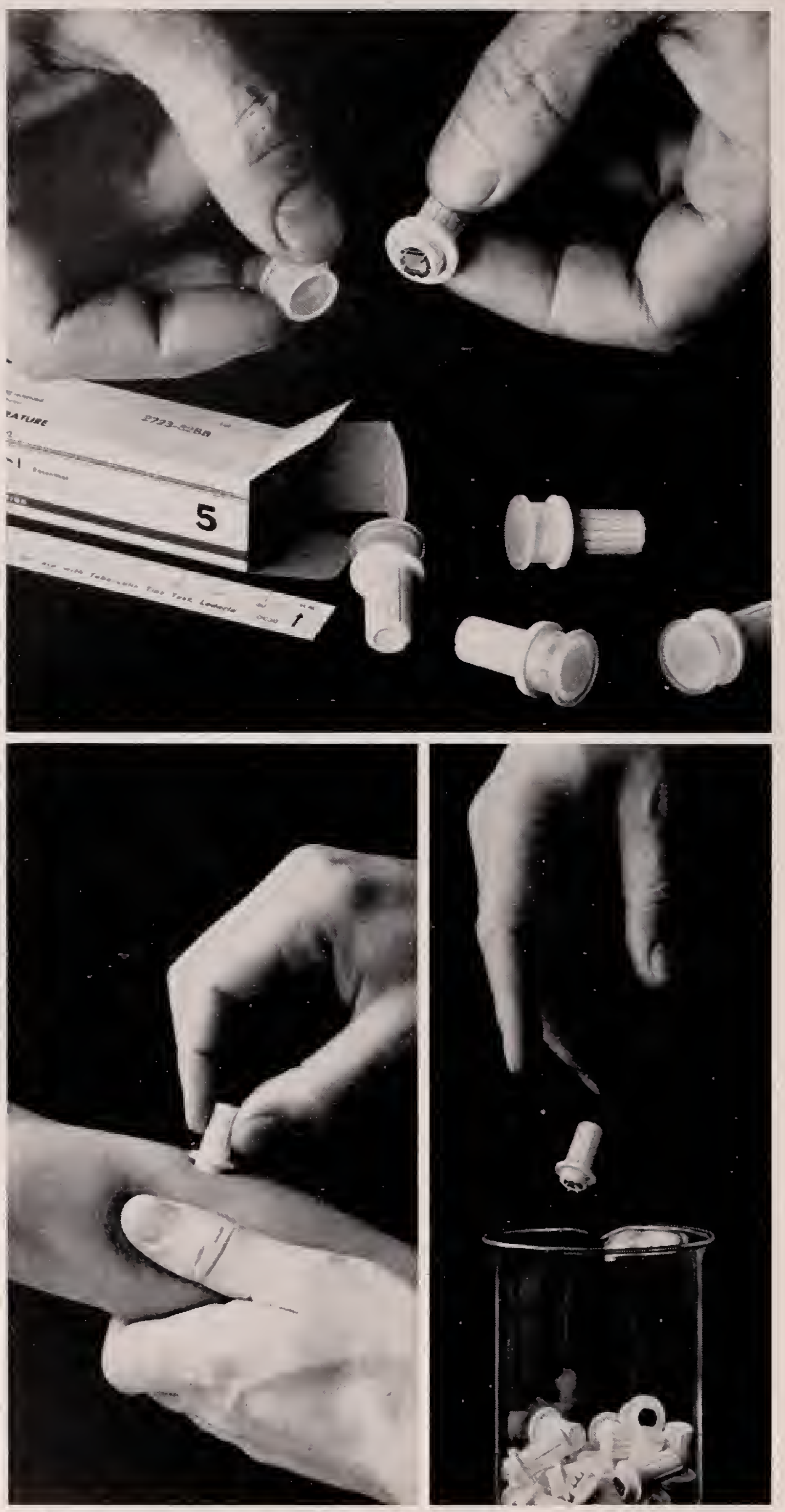
*Section of Pediatrics, Mayo Clinic and Mayo Foundation.

Some people give up their future for gratifications of the moment.—C.O.R.



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Electric Convulsive Therapy and the Narcotic Withdrawal Syndrome

On page 525 of this issue Dr. Harvey Kelman has demonstrated the efficacy of electric convulsive therapy in the suppression of the uncomfortable effects of narcotic withdrawal. As he points out, cases have been reported in the literature in which this form of therapy has been used, but no reports have been forthcoming on this subject since that of Thigpen and associates in 1953.

A number of reasons come to mind as to why electric convulsive treatment of the narcotic withdrawal syndrome has been almost totally discarded in the last 10 years. (1) We have witnessed in these 10 years the advent of the tranquilizing drugs and their efficacy in suppressing the many unpleasant symptoms of the narcotic withdrawal syndrome when used in conjunction with a planned, rational drug-withdrawal program. (2) One is reluctant to use electric convulsive therapy when satisfactory medication can be used instead. Admittedly, this objection has decreased over the past 10 years with the increased ease of administration of electric convulsive therapy and the few contraindications to it. The dangers of electric convulsive therapy have all but disappeared with the use of thiopental sodium and muscle relaxants. There are, however, occasional complications to electric convulsive therapy which often make it a second choice as compared to a tried and true medication program. (3) Theoretically, the confusion caused by electric convulsive therapy does not allow for a good establishment of rapport and communication between the patient and the physician. This rapport is of tremendous importance if the attempted solution of the overall narcotic addiction is to proceed beyond the withdrawal stage. Admittedly this is not too hopeful, as the incidence of recidivism is extremely high in narcotic addiction despite all attempts at any type of psychotherapy.

One may take issue with Kelman's statement of the multiplicity of suggested therapies for the narcotic withdrawal syndrome inasmuch as a rather routine and standard program has been accepted by most physicians engaged in this type of treatment. This can be described briefly as the determination of the stabilization dosage in the first two or three days. Then by calculation the patient may be given a combination of the stabilization dose of his narcotic and a calculated amount of methadone. The original narcotic is then rapidly withdrawn and methadone is substituted. This too is gradually withdrawn so that the entire withdrawal process takes approximately 10 days. An important feature is that the withdrawal program is carried out under the protective umbrella of phenothiazine medication which handles the uncomfortable symptoms of tension during withdrawal.

The time required for this withdrawal program compares favorably with that for use of electric convulsive therapy. In general a narcotic withdrawal program can be completed in approximately 10 to 14 days.

It is good, as Dr. Kelman points out, to reexamine the benefits of a treatment that has been generally discarded, especially when the contraindications have all but been eliminated — as they have for electric convulsive therapy.

Edward M. Litin, M.D.
Rochester, Minn.

Reference

1. Kelman, Harvey: Suppression of the Narcotic Withdrawal Syndrome by Means of Electric Convulsive Therapy. Minn Med, May 1964.

I hope I shall have leisure to make good.—Shakespeare

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MINNESOTA MEDICINE

HONOR AWARD

Minnesota Medicine Medical Writing Awards, 1964

It is the pleasure of the Board of Editors to announce the winners of the third annual Minnesota Medicine Medical Writing Awards chosen from articles published in MINNESOTA MEDICINE during the year of 1963.

The first place plaque is to be awarded to Dr. John I. Coe of the Hennepin County General Hospital for his article "Suicides — A Statistical and Pathological Report" published in the January issue. The presentation will take place during the annual meeting of the Minnesota State Medical Association in Rochester at the New Members, County Officers and Delegates Dinner on Sunday, May 17th.

Certificates for excellence in medical writing will be awarded to the authors listed on the next page together with the titles of their articles which were felt to be particularly outstanding by the Board of Editors.

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MINNESOTA STATE MEDICAL ASSOCIATION

HONOR CERTIFICATE

Manuscript	*Author*	*1963 Issue*
The Battered Child Syndrome	R. B. Raile, M.D. R. W. TenBensel, M.D. Hennepin County General Hospital	October
Histoplasmosis and Histoplasmin Sensitivity in Minnesota	Herman Kleinman, M.D.* Orpha M. LaCroix, R.N. C. Barton Nelson, M.D. Minnesota Dept. of Health and L. Jerome Krovetz, M.D. Gainesville, Florida	April

Minnesota Medicine is honored to have this opportunity to acknowledge the work of its distinguished authors and to express to them applause, thanks and cordial best wishes.

Board of Editors

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*Posthumous

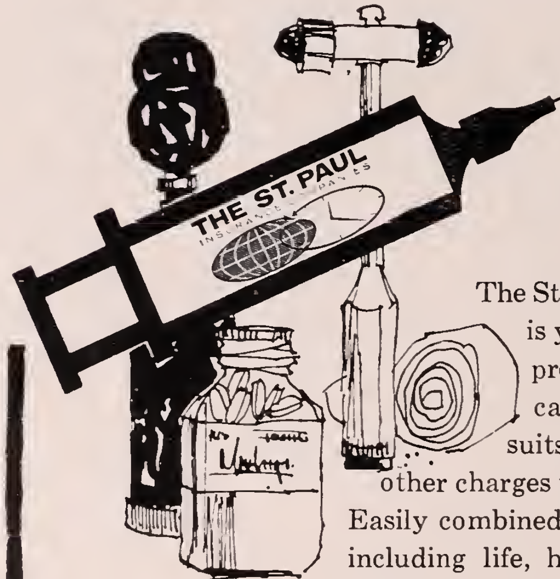
Presidents Letter Continued from Page 499

with a proposal to the legislative commission of the type which reflects their true concern in an unbiased way. We can then give them our whole-hearted support.

The fact that many proprietors of drug stores conduct some business in general merchandise beclouds the issue and should not be part of it, in considering the public welfare in relation to drugs. The pharmacist in these times is not a mere drug clerk, but a skilled and trained professional. If the pharmacists of Minnesota insist on true professional services in transactions involving drugs they will impress the legislators and perform a great service to the residents of Minnesota.

J. P. Medelman M.D.

J. P. Medelman, M.D.
President
Minnesota State Medical Association



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Fifty Years of Honorable Service In Minnesota

The presentation of certificates and pins to Minnesota physicians who have engaged in the practice of medicine for 50 years has become an impressive highlight of each Annual Meeting. According to custom the presentations are made during the course of the Annual New Members, County Officers and Delegates Dinner. Few who have witnessed these ceremonies soon forget the setting of such an occasion at which these colleagues with a half century of medical practice to their credit so alertly respond to the roll call.

The custom of honoring Minnesota physicians who have served their patients and communities for a half century was established in 1942. Forty-one physicians were honored at the first ceremony. This group also included those who have passed the 50 year mark prior to 1942.

To be eligible for this award a doctor must have spent the majority of his 50 years practicing medicine in Minnesota.

In 1964 thirteen doctors were added to the membership rolls of Fifty Year Club.

George I. Badeaux, M.D.

Dr. George Badeaux was born at Brainerd, Minnesota, where he attended high school. He received his medical degree from the University of Minnesota Medical School in 1913 and pursued postgraduate studies at the New York Polyclinic and New York State Postgraduate Schools. He served in the medical corps during World War I and after the war returned to Brainerd, where he has practiced medicine ever since.

Besides being a member of the Masons and Elks Fraternal Organizations, Dr. Badeaux has been a member of the staff of St. Joseph Hospital in Brainerd, at one time chief-of-staff of that hospital. Since 1923 he has been secretary of the Upper Mississippi Medical Society.

Robert L. Bowen, M.D.

Dr. Robert L. Bowen was founder of the Mesabic Clinic in Hibbing, Minnesota. This clinic has continued to operate successfully and has been a credit to the medical profession for many years.

Dr. Bowen was born in Oshkosh, Wisconsin, on August 30, 1887. He graduated from Oshkosh High School and then entered the University of Wisconsin, where he received his B.S. degree.

At Wisconsin Dr. Bowen rowed on the freshman and varsity crew at Poughkeepsie and from this early beginning has continued his interest in water sports.

He received his M.D. degree in 1914 from Rush Medical College, at that time one of the outstanding medical schools in the country. After graduation he obtained additional training in surgery under A. J. Ochsner at Augustana Hospital. During World War I he served one year with the American Red Cross in Poland and thereafter as medical officer in the U. S. Army with the rank of major and chief surgeon of the Colon Hospital in Panama.

Dr. Bowen entered the practice of medicine in Hibbing Minnesota, and assisted in the organization of the Hibbing General Hospital. He was chief surgeon to the Rood Hospital in Hibbing.

He was a member of Psi Upsilon academic fraternity, the Phi Rho Sigma medical fraternity, the American College of Surgeons, and also a member in good standing of the usual state and national medical organizations.

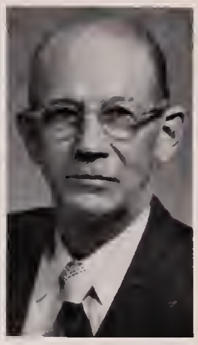
Edward Bratrud, M.D.

Dr. Edward Bratrud was born in Fountain, Minnesota, in 1888. He graduated from Spring Valley High School in 1907 and then attended the University of Minnesota, receiving his B.S. degree in 1911 and his M.D. degree in 1913.

He served his internship at the City and County Hospital in St. Paul and thereafter practiced with his brother in Warren, Minnesota, until 1931. He then organized the Bratrud Clinic in Thief River Falls and remained there until 1959 when he retired from active practice.

He is a member of the usual local and state medical organizations as well as the American College of Surgeons and the American Urological Society.

He spends his summers at Lake Geneva, Alexandria, Minnesota, and his winters in Phoenix, Arizona. He is a member of the Minneapolis Athletic Club.



Lowell M. Campbell, M.D.

Dr. Lowell M. Campbell was born in Miller, South Dakota, Jan. 16, 1886. He graduated from East High School Minneapolis, attended the University of Minnesota and graduated from Rush Medical School, Chicago, Ill. in 1914.

He interned at Northwestern hospital in 1915 and was a member of the regular staff until 1960, then was an honorary member.

Dr. Campbell was Edina Village School doctor and Village Health officer for over 25 years. He retired because of ill health in 1960.

James W. Crump, M.D.

Dr. James W. Crump, was born in Mississippi in 1888 and moved with his parents to Iowa at the age of three. He graduated from the University of Iowa in 1912 and received his M.D. degree in 1914.

He holds a license to practice in Iowa, Colorado, Texas, and Minnesota. In 1923 he moved from Texas to St. Paul, where he has been in general practice up to the present time.

He is on the staffs of Bethesda Hospital, St. Joseph's Hospital, and Children's Hospital.

Elmer O. Dahl, M.D.

Dr. Elmer O. Dahl was born in Minneapolis on June 28, 1891, and received his preliminary education in Minneapolis. He then matriculated at Loyola University, Chicago, receiving his M.D. degree in 1914, after which he served an internship in Chicago.

He served two years in World War I as a medical officer and then did some postgraduate work in otolaryngology. He subsequently came to Minneapolis where he has continued his practice up to the present date.

He is a member of the usual local, state, and national medical organizations, also a member of the Minnesota Academy of Otolaryngologists, the American Academy of Otolaryngology, and the Pan American Society of Ophthalmology. For the past 31 years he has been president of the medical staff of Ebenezer Home.

Richard N. Jones, M.D.

Dr. Richard N. Jones was born in northwestern Ohio in 1884, attending country school and later the Normal College at Marion, Indiana. His premedical and medical work was done at the University of Chicago and the Rush Medical College, from which he received the S.B. and M.D. degrees in 1914.

The next four years he spent time with Dr. George G. Eitel of Minneapolis.

At the beginning of World War I he entered military service, serving as a medical officer at Gettysburg, Pennsylvania, and at the Army and Navy General Hospital in Hot Springs, Arkansas, until the end of the war.

Dr. Jones then began general practice at Gaylord and at Richmond Minnesota, where he remained for eight years before moving to St. Cloud in 1927.

In recent years he has been associated with Dr. C. F. Brigham, Jr.

He is a member of the Stearns-Benton, Minnesota, and American Medical Associations, American Academy of General Practice, and American College of Surgeons.

Norman M. Keith, M.D.

Dr. Norman M. Keith was born in Toronto, Ontario, Canada, on June 8, 1885. He attended the University of Toronto and the Johns Hopkins University, which granted him the degree of doctor of medicine in 1911. In 1916 he became a member of the Royal Army Medical Corps of the British Expeditionary Forces, returning to civilian life in 1919.

Dr. Keith came to Rochester, Minnesota, in October, 1920. On July 1, 1921, he was made joint head of a section of medicine and on January 1, 1923, head of a section. He was appointed an assistant professor of medicine in the Mayo Foundation, Graduate School, University of Minnesota, in 1920, and was advanced to asociate professor in 1922 and professor in 1936. On April 1, 1936 he became a senior consultant in medicine, and retired from the staff of the Mayo Clinic on December 31, 1950.

He contributed more than 100 papers to the medical literature.

Katherine A. Nye, M.D.

Dr. Katherine Ann Nye was born in Zumbrota, Minnesota, on February 27, 1887. After finishing her public school education she entered the University of Minnesota, receiving her B.S. degree in 1912 and her M.D. degree in 1914. Thereafter she served her internship at the New England Hospital for Women and Children in Boston, Massachusetts, and served for a period in Women's Hospital in Philadelphia.

She subsequently located in St. Paul, where she has been in private practice since 1915.

She has been interested in a large number of civic organizations and has been a member of the staffs of Bethesda Lutheran Hospital, Children's Hospital, St. Luke's Hospital, Miller Hospital, St. Paul, and Divine Redeemer Memorial Hospital of South St. Paul.

She has served as a medical examiner for the Minnesota Bureau of Health and the Ramsey County Juvenile Court, and has been cited as one of the members of Who's Who in Minnesota and Who's Who of American Women.

Dr. Maurice Shillington was born in Omaha, Nebraska, on May 30, 1891, and received his education there in the public schools through the twelfth grade. He then enrolled in Creighton University from which he received a degree of Doctor of Medicine in April, 1914. On May 1, 1914, he started an eighteen-month internship at the Northern Pacific Beneficial Association Hospital in Brainerd, Minnesota, continuing with this medical organization for 39½ years.

In 1927 he became a diplomate of the American Board of Internal Medicine, and in 1928 was accepted as a fellow in the American College of Physicians.

In 1938 he was asked to become Chief-of-Staff of the Northern Pacific Beneficial Association Hospital in Glendive, Montana. Realizing that Montana had no Blue Shield, he became active in establishing one and served as its president for the first six years. He later was president of the Montana State Medical Association.

Returning to Minnesota, he joined the staff of the University Health Service where he remained until his recent retirement.

M. A. Shillington, M.D.

Dr. Olof Sohlberg was born in St. Paul on January 15, 1892.

He entered the University of Minnesota and at the age of 20 received his B.S. degree, and two years later his M.D. degree.

After graduation he practiced with his father for one year, and then entered the medical corps of the United States Army and saw service in the American Expeditionary Force in France.

Dr. Sohlberg has been in general practice with special emphasis on surgery and has been a member of the American College of Surgeons since 1931. He has taken an active part in the Minnesota Blue Shield plan and served as the first president for a period of two years. He currently serves in the capacity of secretary of the board of directors of this organization.

He has been a member in good standing of the usual county, state, and national medical organizations, also a member of the staff of Bethesda Lutheran Hospital, Children's Hospital, and St. John's, St. Luke's, and Miller Hospitals.

Olof I. Sohlberg, M.D.

Dr. Carl A. Traeger was born in 1889 and graduated from the University of Minnesota in 1914. During World War I he served as a first lieutenant in the United States Army Medical Corps. He practiced continuously in Faribault, Minnesota, until 1959 and is now retired.

He was formerly associated with Drs. S. B. Haessly and A. M. Hanson.

Carl A. Traeger, M.D.

Dr. Herbert M. Wynne was born in Norfolk, Virginia, in 1887, and received a B.S. and an A.M. degree at Bethany College in 1906-1907. He did graduate work at Ohio State University in 1909 and 1910 and then transferred to Johns Hopkins University, where he received his M.D. degree in 1914.

He became a reserve officer in the medical corps and saw active service in World War I, advancing from first lieutenant to captain. At the end of the war he came to Minnesota and has remained here ever since. He became a clinical assistant instructor and finally an associate professor in the department of gynecology at the University of Minnesota.

He retired from active practice in 1958.

Dr. Wynne has been a member of the usual medical societies in addition to many medical organizations in the field of obstetrics and gynecology. He was on the editorial staff of the Journal-Lancet and was also a contributor to Lewis Surgery.

Herbert M. N. Wynne, M.D.

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Cardiac Catheterization

QUESTION: How painful and dangerous is cardiac catheterization?

M.D., Minneapolis

ANSWER: Except in unusual circumstances or in very poor risk patients, cardiac catheterization is a safe procedure for the usual patient. The risk is certainly so minimal that physicians should encourage patients to undergo the study when this is indicated. Although no over-all nation-wide statistics are available, the mortality rate is probably less than 1 per 1000. Several series of 2000-3000 studies with no deaths have been reported.

The matter of "pain" is subjective to the patient. The only discomfort is the injection of local anesthesia into the site of future catheter induction. This is the same as a "cut-down." There is no pain in the intracardiac movement of the catheter. A sensitive patient may become alarmed by the sensation of extra systoles during manipulation but reassurance usually suffices. Angiocardiography elicits a temporary "hot" flush which is momentary. The usual complaint is not referable to the cardiac catheterization per se but rather to the prolonged immobility in one position. Even this can be ameliorated by small changes in posture, exercise tests, etc.

With proper operative sedation, the usual patient (children especially) doze through the procedure. Local anesthetic is, therefore, the anesthesia of choice and often necessary to obtain complete studies.

Susceptibility to Pulmonary Tuberculosis

QUESTION: Have any observations been made indicating that a particular type of body-build is associated with an increased susceptibility to pulmonary tuberculosis?

M.D., New Ulm

ANSWER: Statistics available for large groups from records of World War II veterans clearly indicate that tall, thin men developed tuberculosis more frequently than men of other physical types. In one group of 54,000 Navy recruits studied it was shown that active disease was four times as great in tall, thin men as in other body types. Of course these findings are concerned with a select patient population group.

Tobacco

He is an expert surgeon, brilliant pathologist, and an uncanny diagnostician, but he is somewhat rusty on advanced cigarette testimonials.—Morris Fishbein

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Because it's a pure chemical substance. Therefore, you are assured of unvarying potency, uniform activity and predictable response. It is "The thyroid hormone preparation now recommended as superior because of purity, stability, accuracy and rapid absorption by mouth..."* The human thyroid secretes levothyroxine—SYNTHROID Tablets are sodium levothyroxine. In short, it's pure thyroid hormone replacement therapy.

Indications: Conditions of the hypothyroid state.

Precautions: As with other thyroid preparations, an overdosage may cause diarrhea or cramps, nervousness, tremors, tachycardia, and continued weight loss. Medication, in such cases, should be stopped for 2-6 days, then resumed at a lower level. In patients with diabetes mellitus, careful observations should be made for changes in parameters that are used to guide antidiabetic therapy.

Contraindications: Thyrotoxicosis, acute myocardial infarction.

Administration and Dosage: Administer as a single daily dose, preferably after breakfast.

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*Starr, P.: In Conn, H.F.: Current Therapy, Philadelphia, W. B. Saunders Company, 1962, p. 315

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Fracture–Trauma Conference

Fractures of the Posterior Lip of the Distal Tibia

Fracture of the posterior lip of the distal tibia ("the posterior malleolus") is a relatively common feature of ankle fractures. Ordinarily it occurs in association with a fracture of the lateral malleolus and occasionally with a fracture of both the medial and lateral malleoli. The mechanism of injury is a backward and lateral displacement of the foot on the leg, usually associated with external rotation of the foot and ankle. The posterolateral aspect of the distal tibia is the site of the fracture.

The most important consideration in this fracture is posterior stability of the ankle joint. If the fragment is small enough so that the curve of the distal tibia in the lateral projection is adequate to prevent posterior displacement of the talus, closed reduction will ordinarily suffice. In this situation, even absolute anatomical reduction is not completely necessary. The rule is that if the posterior fragment is less than one third of the articular surface of the tibia, open reduction is not necessary. In some cases, the fracture involves a third of the articular surface, but is associated with very little displacement. Closed reduction may return this type fracture to good position, and it is then acceptable to treat the fracture in this manner. It is necessary, however, to watch this fracture very carefully with follow-up X rays at frequent intervals to assure that the position is maintained.

Methods of Reduction

Closed Reduction

The method of closed reduction which is ordinarily used is to dorsiflex and evert the foot and ankle on the leg. It is often helpful to dorsiflex the great toe also. The reason for this is that the flexor hallicis longus tendon passes directly across the posterior fragment and by stretching this tendon the fragment can frequently be pulled down into place very nicely.

In most fractures of this type, closed reduction should at least be attempted. If the reduction by closed means is not satisfactory, the surgeon should be prepared to proceed with open reduction and internal fixation.

Open Reduction

The indications for open reduction and internal fixation of this fracture are three:

Continued

1. Following closed reduction, there is any residual posterior subluxation of the talus.
2. Following closed reduction, the fragment loses position in the cast.
3. The fragment involves more than one third of the articular surface of the tibia.

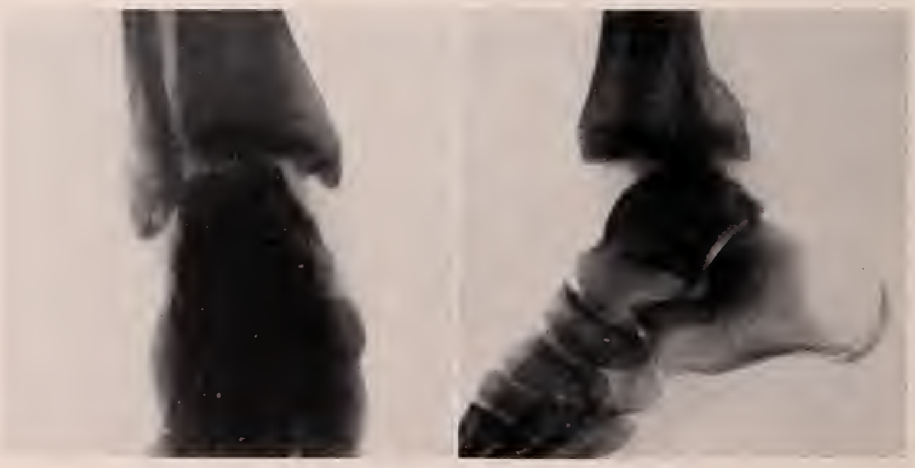
The reason that one third, or as sometimes stated, two fifths of the articular surface is so important is twofold. First, enough of the articular surface is involved so that less than anatomical position may result in a roughness of the articular surface, with subsequent development of very severe early traumatic arthritis in the ankle joint. Second, the development of posterior subluxation of the talus on the tibia or any residual subluxation will also result in rather severe disability.

Technique of Open Reduction

It is best to have the patient in the prone position for the open reduction of this fracture. The exposure ordinarily is made through a posterolateral incision parallel to the tendo calcaneus. Some authors prefer a posteromedial incision, but it has been found that the posterolateral incision gives a much more direct approach. By dorsiflexing the foot with the bone exposed, the posterior lip of the distal tibia can be reduced into position and held in place with a towel clip. Holding the fragment in reduced position, a drill hole is placed with a 9/64 drill. The drill point only traverses the posterior fragment. A single, self-tapping screw is then placed from posterior to anterior across the fracture site. It is important to have the screw extend parallel to the ankle joint and through the anterior cortex of the tibia in order to obtain good fixation.

The associated lateral and/or medial malleolus fracture may be reduced manually. Frequently, a medial malleolar fracture is best treated by screw fixation. The lateral malleolus can be fixed with an intramedullary pin to afford added stability.

After reduction, either open or closed, a cast from toes to groin is applied. The knee is held in 20 degrees flexion. The foot is held in neutral position with the ankle at 90 degrees. Without internal fixation of the malleolar fracture, slight inversion of the foot is necessary to hold the reduction.

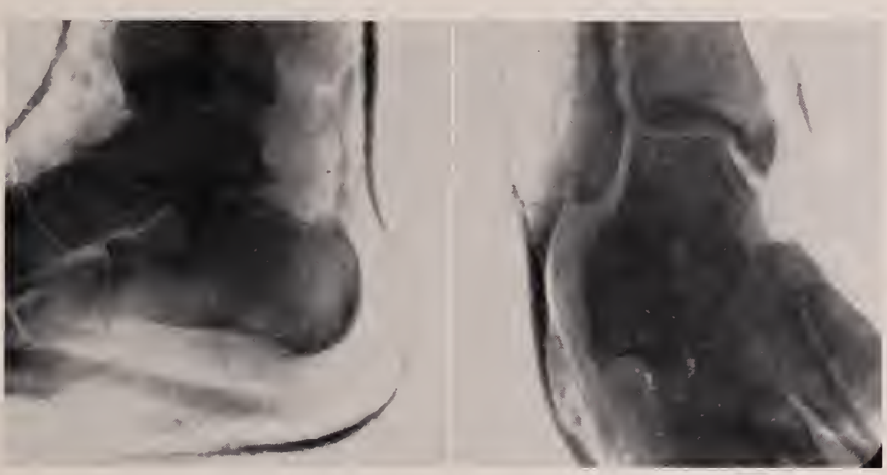


Case 1 Original X rays before treatment — anterio-posterior, lateral.

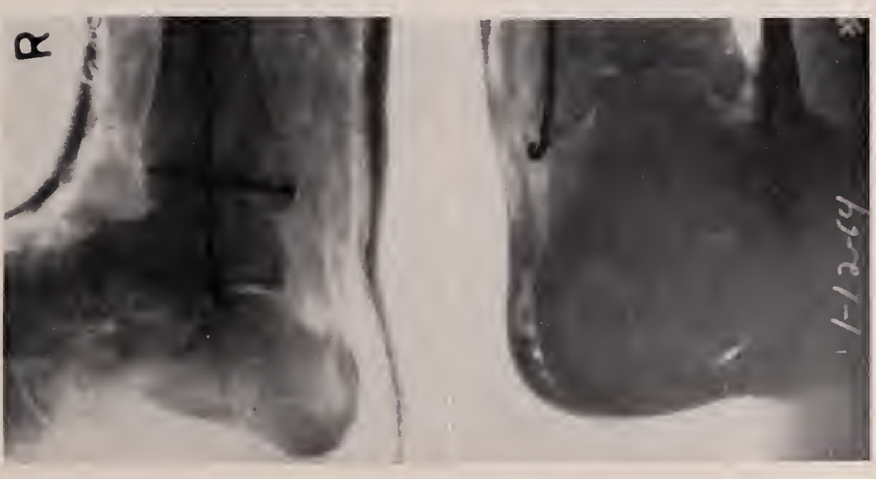
X-ray films of the ankle in the anterio-posterior, lateral, and internal oblique projections should be taken immediately in the operating room, the day following reduction, and at weekly intervals during the first three weeks after reduction. At six to eight weeks, a short leg cast may be applied and at 12 weeks, a new short leg walking cast. Usually this fracture will take from 12 to 16 weeks to heal well enough so that plaster immobilization can be discontinued. After final removal of the cast, it is often useful to apply a Gelocast boot for two to three weeks in order to support the circulation of the leg as the patient resumes full weight bearing without external support.

Case Reports

The first case is that of a 16-year-old boy who sustained a fracture of the posterior aspect of the distal tibia as well as a fracture of the lateral malleolus. The posterior tibial fragment involved just one third of the joint. Closed reduction was attempted under anesthesia. The follow-up X rays showed that there was a residual posterior subluxation of the talus on the tibia. For this reason, the fracture was opened and internally fixed with a single screw. An intramedullary pin was used to fix the lateral malleolar fracture.



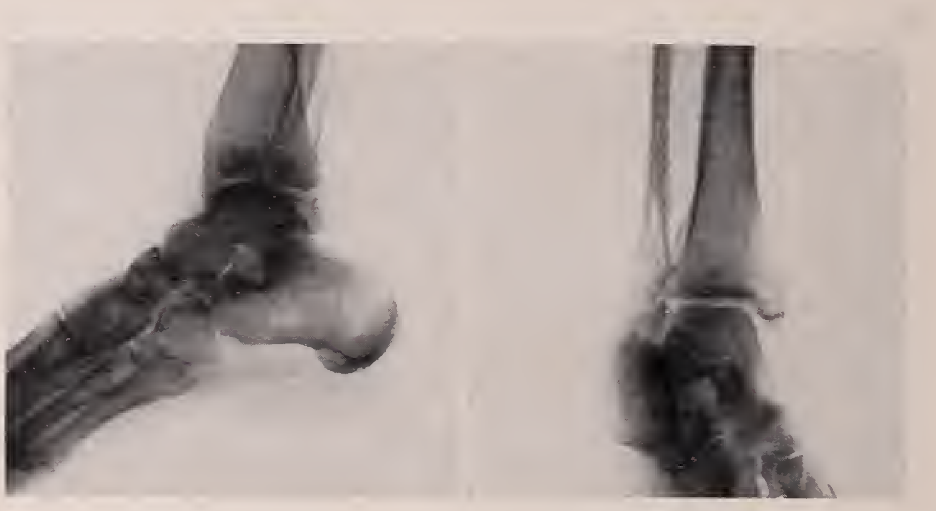
Case 1 Anterio-posterior, lateral X rays after closed reduction.



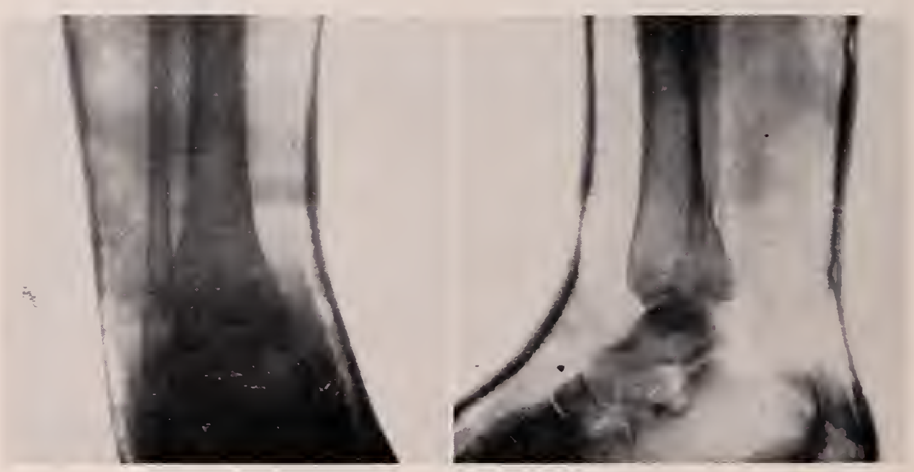
Case 1 X rays after open reduction.

Continued

The second case is that of a 40-year-old housewife. In her case there was relatively little displacement of the posterior tibial fragment, although there was lateral subluxation of the talus on the tibia. Closed reduction brought the fragment within a millimeter of anatomical position. This fracture was treated in a closed manner and position was maintained in plaster. If any displacement of this fragment had been noted on follow-up X rays, open reduction would have been done.



Case 2 Original X rays anterio-posterior and lateral.



Case 2 X rays after closed reduction.

Summary

In summary, the fracture of the posterior lip of the distal tibia can be treated by closed or open methods. Rather well-defined criteria are available as indications for open reduction. Occasionally, a large fragment can be treated in a closed fashion if there is not a significant amount of original displacement and a reduction is anatomical. Small fractures in this area, involving a small amount of the joint surface, do not cause residual ankle disability.

Joseph M. Tambornino, M.D.
Minneapolis, Minn.

Tumor Conference

Malignant Melanoma in Pregnancy

N. T., aged 29, presented herself in November 1963, at one month pregnancy for consideration of a therapeutic abortion. On June 1, 1962, a pigmented mole was removed from the medial side of the popliteal area of the left leg. No obvious incision was made through the tumor, but a very thin margin of normal skin was found. The pathologic diagnosis was superficial malignant melanoma with no invasion of the corium.

On June 11, 1962, re-excision of the original area with four inches margin on all sides, including the popliteal tissue, was done in continuity. Immediate split thickness of skin graft and simultaneous left groin dissection was done. No residual tumor was found in the local region or in the excised node-bearing area. Repeated follow-up examinations revealed no evidence of local, pulmonary, glandular, liver, cardiac, brain or other metastases.

The Problem

Consideration of the possibility of recommendation for therapeutic abortion based on the possible stimulating effect of pregnancy upon possible residual or metastatic malignant melanoma cells.

Discussion and Brief Review of Literature

Pack[5] reports that malignant melanoma during pregnancy appears at a more advanced stage than the general average, with lymph-node or other metastases being present approximately twice as frequently. When treated and comparison made with the results of treatment at similar stages (definite curability), the results are the same. Furthermore, there are many long-term survivors in precisely the identical situation of this patient, i.e., becoming pregnant after previous surgical treatment of malignant melanoma. It has been estimated but not proved that there is a three times greater tendency for a mole to become malignant while a woman is pregnant than when not pregnant.

McCune[4] states that termination of pregnancy when melanoma is found is of very questionable value; he believes that quick and adequate treatment of the lesion is more important than the possible influence of pregnancy.

Continued

Ackerman[1] cites Pack's statement that pregnant women who develop malignant melanoma have a poor prognosis. Nor is any evidence presented for a recommendation that once the melanoma is present the termination of pregnancy will give the patient a better prognosis. Wright[8] states that the adverse effect of pregnancy on melanoma is well known, but he presents no evidence for analysis.

Treatment

Ideally, a wide local excision including en bloc intervening tissue with skin and fascia to and encompassing the immediate lymph-node drainage area should be done to obtain best results. Pack[5] recommends an amputation for extremity melanoma if the nodes are positive and the lesion is located too far distal for proper en bloc dissection.

Some authors suggest a two-week waiting period for clearance of intervening lymphatics; others[7] recommend immediate node dissection.

Prophylactic node dissection is recommended by Ackerman,[1] Lund,[3] McCune,[4] Royster,[6] and Pack.[5] Clinically, local lesions produce some 20% to 40%[5] to 50%[4] positive nodes as reported in various series.

The small size of a melanotic lesion (less than two centimeters)[3] carries longer survival, and very superficial lesions have a high survival rate.[3] Palpable metastatic nodes have a very grave prognosis with only a 5% chance of a five-year cure.[1] If an inadequate incision is done primarily, then 50% have positive nodes and a high local recurrence rate when seen at a later date for treatment.[6] Five-year survival rates of women under 50 without node involvement are 74%.[8] Absolute survival[2] of stage one or two (without positive nodes) is 46.1% for five years and 11.3% for 10-year-cure expectancy.

Conclusions and Recommendations

Although pigment tissue seems to be activated during pregnancy, it is not certain that pregnancy actually stimulates a malignant melanoma. Evidence could, however, be interpreted in this way. There is no evidence presented that subsequent pregnancies are deleterious and obviously would be of no significance if tumor did not exist. This patient had a superficial lesion, negative lymph nodes, and is a female under 50. Therefore, one can expect an excellent outlook for cure. Although the interval between initial lesion and the present problem is only one and one-half years, there is at least no evidence of existing tumor at this time. Therapeutic abortion is not recommended for this patient and is even of very doubtful value when malignant melanoma develops during pregnancy.

Comments

The problem presented in this Tumor Conference has two facets which should be considered: (1) the initial definitive treatment, and (2) the present problem. I concur completely in the primary treatment of this patient with one small and certainly debatable reservation. The initial diagnosis was established with the removal of a pigmented lesion with a narrow margin of excision. There is no reason to extend this initial operation, for it is unnecessary if it is benign, and probably inadequate if a malignant melanoma becomes the established diagnosis. The subsequent re-excision of the area was quite properly performed. My only variation with the technique as presented would be either to have delayed the regional node dissection or to have performed it in continuity if such were technically possible; and it would seem to me it would be in this particular situation. Unless an excision and dissection in continuity can be performed, I would prefer to wait ten to fourteen days before proceeding with the regional node dissection.

There is no good evidence that I know of, and none in my own experience, to support the fact that therapeutic abortion offers any improvement in the salvage rate of patients who present themselves with simultaneous malignant melanoma and pregnancy. I completely concur with the recommendation of the tumor committee.

Harry W. Southwick, M.D.
Chicago, Illinois

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This Epitaph

Here lies Philip Theophrastus, the excellent doctor of medicine who with marvelous skill cured those bad wounds, leprosy, podagra, dropsy and other incurable diseases of the body and honored his possessions by distributing them among the poor. In the year 1541 on the 24th day of September he exchanged life for death.*

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*Gout in the feet.

You May Stub Your Toe

You will never stub your toe standing still. The faster you go the more chance there is of stubbing your toe, but the more chance you have of getting somewhere.

—Charles F. Kettering

Paracelsus'

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Clinical Path Conference

Fever, Pancytopenia and Lip Ulcer

A 32-year-old white woman was admitted to the hematology service on November 18, 1962. She had been well until early September, 1962, when pain, swelling and erythema of the right calf developed. A diagnosis of thrombophlebitis was made, and she was treated with elevation and support of the leg. One week later, fever appeared for the first time and persisted until admission. The fever was remittent (up to 102 to 104° F. daily) and occasionally was associated with shaking chills. With the onset of fever an ulcer appeared over the central portion of the lower lip and persisted. Blood findings by her home physician were consistent with pancytopenia. Bone-marrow findings were not diagnostic. The past medical history was unremarkable. A diagnosis of lymphedema praecox had been made at the Mayo Clinic in 1954.

Physical Findings

On physical examination the patient appeared acutely ill. The blood pressure was 110 mm. of mercury systolic and 60 diastolic, pulse rate 134 per minute and temperature 104° F. A crusted lesion measuring 0.5 cm. by 0.5 cm. was observed over the lower lip. The pharyngeal mucosa was reddened and small white patches suggestive of thrush were evident. The heart rate was accelerated but no enlargement or significant murmurs could be found. The spleen descended two fingerbreadths below the left costal margin with inspiration and was soft. Grade 2 lymphedema of both lower extremities was observed.

Laboratory Findings

Initial laboratory findings were as follows: hemoglobin 9.9 gm./100 ml. of blood; erythrocyte count 3,130,000, and leukocyte count of 1600/cu. mm., with a differential count of 60 per cent lymphocytes, 2 per cent monocytes, 29 per cent segmented neutrophils, 1 per cent eosinophils, 2 per cent metamyelocytes, 2 per cent late myelocytes, 2 per cent early myelocytes, 1 per cent progranulocytes, and 1 per cent blast cells; 13 normoblasts per 100 leukocytes; platelet count 83,000/cu. mm.; reticulocyte count 9.8 per cent; grade 2 anisopoikilocytosis, increased polychromasia, myeloid im-

Continued

maturity and scattered normoblasts in the peripheral blood; erythrocyte sedimentation rate 88 mm. in one hour (Westergren method); and urinary findings normal.

X-ray examination of the chest did not show any abnormality.

Discussion of Case

Dr. Murray N. Silverstein:

I attended this patient. She appeared extremely ill. The problem was that of fever of undetermined origin in a young woman with splenomegaly and pancytopenia. The pancytopenia afforded an important diagnostic clue.

Differential Diagnosis

Differential diagnosis of this hematologic entity should include:

(1) Primary blood dyscrasia such as acute leukemia and aplastic anemia.

(2) Infiltration of the marrow by carcinoma cells and infrequently by lymphoma.

(3) Metastatic invasion of the marrow by tuberculosis or disseminated fungal infection, and

(4) Lupus erythematosus. Causes such as multiple myeloma, pernicious anemia, paroxysmal nocturnal hemoglobinuria and primary hypersplenism seemed unlikely in this patient.

Clinically we were unable to uncover a toxic exposure as a basis for aplastic anemia. The only drug the patient had taken recently was tetracycline. Rarely we have seen leukopenia or thrombocytopenia, but never pancytopenia, associated with the use of this agent. The presence of splenomegaly and reticulocytosis suggested that aplastic anemia was unlikely in this patient.

Pancytopenia has been observed in disseminated lupus erythematosus. Hematologically, in this disease we have seen mononuclear leukopenia most frequently, thrombocytopenia next in frequency, and overt hemolytic anemia infrequently. The degree and duration of fever observed in this patient seemed quite unusual for disseminated lupus erythematosus. Dr. Martin, would you comment on this?

Lupus Erythematosus

Dr. William J. Martin:

Lupus erythematosus is a cause of intermittent fever, often as an early manifestation. As the disease progresses, constitutional manifestations including fever may become more prominent. Of course, remission of all signs including fever may ensue and persist for long periods.

The exact genesis of fever in a patient with lupus erythematosus is unknown. However, experimental data appear to support the concept of tissue injury in the production of fever, at least under some circumstances, wherein a product or products liberated from injured tissues act on the thermoregulatory centers in the regions of the hypothalamus and brain stem and disturb their function. Consequently, neural mechanisms are initiated which are responsible for the vasomotor and muscular phenomena that result in both increased heat production and decreased heat loss. Such a concept is given in explanation of the febrile response associated with infection, inflammation, neoplasia, hemolytic crises, vascular accidents (both hemorrhage and infarction), mechanical injuries, and so forth.

Microbial Pyrogens

By positive transfer methods, two distinct pyrogens can be isolated from the serum of rabbits injected intravenously with microbial pyrogens. The microbial pyrogens include endotoxin derived from gram-negative enterobacilli, viruses such as those of the influenzal group, and tuberculin. The first serum pyrogen is cleared rapidly from the bloodstream after the injection and is indistinguishable from the microbial (exogenous) pyrogen injected. The second, appearing later, has all the characteristics of leukocytic (endogenous) pyrogen; that is, second serum pyrogen appears to be identical with the pyrogenic substance produced by saline extraction of polymorphonuclear leukocytes.

There is something in inflammatory exudates which on injection into normal subjects can result in fever; one source of such a pyrogen is polymorphonuclear leukocytes.

Of course, in any patient with lupus erythematosus, one should be as certain as possible that the fever is not more a manifestation of an associated process, such as infection. Dr. Silverstein, what about your further differential diagnosis?

Lymphoma

Dr. Silverstein:

When lymphoma is associated with pancytopenia the latter usually results from previous therapy or bone-marrow invasion by lymphoma. Hodgkin's disease involving only the marrow is extremely rare. The clinical picture in this patient certainly is reminiscent of that of many patients we have seen with abdominal lymphoma. The blood changes might be explained on the basis of hypersplenism. Bone-marrow examination would be quite helpful in this situation.

The combination of myeloid immaturity and normoblasts in the peripheral blood along with anemia defines a leukoerythroblastic blood picture. We have seen leukoerythroblastic blood smears most frequently in association with acute leukemia, metastatic carcinoma, myeloproliferative states such as agnogenic myeloid metaplasia, and severe sepsis.

Metastatic Carcinoma

The presence of fever has been noted in patients with metastatic carcinoma. Splenomegaly, however, seldom is associated with carcinoma. We have seen a few cases of breast carcinoma with metastasis to the spleen. Infrequently also, a pancreatic carcinoma with thrombosis of the splenic vein may produce splenomegaly. Carcinoma as the cause of this patient's problem seems unlikely.

Leukemia

We are left then with two other considerations. The first is acute leukemia. The entire clinical course would fit that of acute leukemia. Bone-marrow examination would be extremely helpful in establishing a diagnosis. Fever occurs in at least 50 per cent of the cases of acute leukemia.

Continued

Shaking chills, however, are not common in this disease and should suggest an infectious complication. Dr. Martin, what has been your experience with fever associated with acute leukemia?

Dr. Martin:

In acute leukemia, unlike chronic leukemia, fever may be "primary"; however, in all cases, infection must be excluded. The increased incidence of infection including bacteremia in acute leukemia emphasizes the undesirability of hasty conclusions that a given fever is "primary." Infection appears responsible for about two thirds of the febrile episodes in patients with acute leukemia and causes death as often as does acute hemorrhage.

In patients having hematologic disease, including acute leukemia, bacteremia often develops without precipitating factors such as an antecedent operation, and consequently the portal of entry frequently is inapparent. The converse generally is true of bacteremia not associated with hematologic disease.

Defective polymorphonuclear response in acute leukemia, chronic granulocytic leukemia, and aplasia or agranulocytosis may predispose to infection; in chronic lymphocytic leukemia, lymphoma and multiple myeloma, defective gamma-globulin may so predispose.

Disseminated Infection

Dr. Silverstein:

The other possibility I considered strongly in this case was that of a disseminated infection such as miliary tuberculosis or histoplasmosis. Fever and splenomegaly have been seen in both. Tuberculosis has been the cause of more than one hematologic headache. We have seen both lymphatic and myeloid-leukemoid reactions in this disease. We have observed acquired hemolytic anemia associated with thrombocytopenia in one patient with tuberculosis. We have also noted a clinical picture produced by tuberculosis which was indistinguishable from that of agnogenic myeloid metaplasia. Others have commented on the association of tuberculosis with leukemia.

Disseminated histoplasmosis as a cause for leukoerythroblastic blood picture has not been appreciated in the past. We have seen this on at least three occasions. In two patients we cultured Histoplasma directly from the marrow. Dr. Martin, with the negative chest X-ray findings, is miliary tuberculosis unlikely in this patient?

Dr. Martin:

Miliary tuberculosis may occur without positive findings, physical and radiographic, insofar as the chest is concerned; but this is unusual. Generally, one should be reluctant to consider miliary tuberculosis as a strong possibility if roentgenograms of the thorax are not revealing.

Dr. Silverstein:

Dr. Martin, what do you think about the persistent lesion of the lip in this case?

Dr. Martin:

Ulcerative lesions on the lip and fever suggest the possibility of herpes simplex, which may be unassociated with other diseases or perhaps secondary to a bacterial infection such as pneumonia. Also, in herpes simplex, there may be only the local lesion or systemic involvement such as meningoencephalitis. In addition, one should consider the possibility of acute leukemia, and likewise histoplasmosis, especially if the lesions also involve the buccal surface. Many causes of lesions of the lip of course have special interest to dermatologists, but do not require review in this instance.

Dr. Silverstein:

My impression in this case narrowed down to two possibilities: acute leukemia and disseminated infection such as histoplasmosis.

Bone-Marrow Findings

The bone-marrow examination showed a myeloid-erythroid layer of less than 1 volume per cent (normal, 4 to 7) and a fat layer of 1. Such volumetric measurements are associated with an extremely hypocellular preparation, but the normal fat layer is not usual in aplastic anemia. The bone-marrow smears were hypocellular. Erythrogenesis was normoblastic and more active than genesis of other lines. Some large immature erythrogenic forms were observed. Myelopoiesis was inconspicuous and toxic. A few megakaryocytes were seen. Sections of bone marrow revealed a reduction in erythropoiesis and myelopoiesis with a relative increase of megakaryocytes showing degenerative nuclear change. A few tiny foci of normoblasts were observed. The reticulum was markedly stimulated. Biopsy with a Vim-Silverman needle showed features essentially similar to those on bone-marrow section. These changes were considered most likely to be a result of a toxic effect. The marrow was certainly not that of acute leukemia.

Dr. Martin:

Under the circumstances, did you consider the lip lesion?

Biopsy of Lip

Dr. Silverstein:

With acute leukemia unlikely we directed our attention to the lip lesion and took a generous biopsy specimen, which revealed numerous *Histoplasma organisms*. Dr. Martin, what would you say about therapy in this patient?

Treatment

Dr. Martin:

Amphotericin B is proving to be an effective drug against deep-seated mycotic infections. Against susceptible yeast and fungi, it is fungistatic rather than fungicidal. It has caused sputum conversion in patients with

Continued

chronic cavitary pulmonary histoplasmosis and has produced arrest or cure of severe, disseminated histoplasmosis. Since there is only minimal absorption of amphotericin B after oral administration, it is given intravenously for systemic infections. The drug is administered intravenously in a single daily dose that varies from 0.25 to 1.0 mg./kg. of body weight. Treatment is begun with an initial dose of 0.25 mg./kg. Although the infusion is usually given daily, intolerance on the part of the patient may require reduction to every other day. Continuation of therapy for several weeks is usual, but data are lacking to establish precisely the optimal amounts of the drug or duration of therapy. One attempts to increase gradually in amounts of 10 mg., the quantity of the drug being administered to approximately 1 mg./kg. of body weight daily, depending on the tolerance of the patient.

Complications of Treatment

Phlebitis at the site of administration, flushing, chills, fever, headache, vomiting, dyspepsia, diarrhea, anemia, hypocalcemia, respiratory distress, and anaphylactoid reaction with occasional peripheral cyanosis, and azotemia may result from administration of amphotericin B. Most patients show increasing azotemia after prolonged therapy with higher doses of the drug, and this effect is the chief limiting factor in the doses which may be employed. Renal function should be determined regularly during therapy. In our experience, administering the medicament over a longer period, decreasing the total daily dose, and stopping treatment for a few days have each been effective in controlling most side effects. It is preferable to adjust the dosage to obviate renal damage and to prolong the time of treatment rather than to use higher doses productive of toxicity. When therapy is stopped for a period of days, it is resumed with a lower dose and increased gradually to the optimal level. Aspirin, antihistaminics, and epinephrine also may help control such untoward reactions. Corticosteroids likewise have been recommended by some investigators in this regard.

Dr. Silverstein:

We started therapy on the day we received the report of the positive biopsy findings. At that time also, blood cultures were positive for Histoplasma. Unfortunately, with the patient's weakened defenses, superimposed bacteremia with Staphylococcus aureus and Streptococcus mitis developed. Thrombophlebitis again occurred, with embolization to the lungs. The patient went into coma and died six weeks after admission. Dr. Bahn, would you give the necropsy findings?

Post-mortem Observations and Conclusions

Dr. Robert C. Bahn:

Post-mortem examination revealed hypoplastic bone marrow. Multiple abscesses were present in the lungs, kidney, spleen and liver. Histologically, these abscesses contained gram-positive cocci but cultures were negative. No granulomas were identified in the visceral organs. The lymphoid tissue of lymph nodes and spleen was hypoplastic. A thrombus was present in the left middle cerebral artery and was accompanied by a recent infarct in the distribution of this artery and by a recent hemorrhage in the region of the basal ganglia extending into the midbrain.

Dr. Silverstein:

Dr. Martin, would you comment on the inability to find Histoplasma at necropsy?

Dr. Martin:

Since H. capsulatum was demonstrated microbiologically, both by biopsy of the lesion and by blood culture, I have no doubt that the patient had histoplasmosis. Since she was given amphotericin B in maximal amounts for longer than two weeks, one can only conclude that the antibiotic was responsible for eradicating the organism.

Dr. Silverstein:

This patient had polymicrobic bacteremia. What are the principles of management of this problem?

Dr. Martin:

Patients with polymicrobic bacteremia may require administration of several drugs simultaneously. As it is difficult to say which organism is most important in polymicrobic bacteremia, one gives broad coverage. However, one attempts to keep the number of agents minimal and rarely resorts to a so-called antibiotic umbrella. In this instance, probably therapy of any kind would not have been curative, but as a theoretic answer to your question, one probably would have given methicillin because of the Staph. aureus, at least until the results of in vitro bacterial susceptibility studies were available. Ordinarily one gives penicillin G with or without conjoint administration of streptomycin for bacteremia due to Strep. mitis. Although methicillin has some effect against streptococci, probably in the case of bacteremia one would hesitate to rely on that agent for its antistreptococcal effect and would give penicillin G along with the methicillin in an attempt to eradicate the Strep. mitis.

If the patient were allergic to penicillin, therapy of polymicrobic bacteremia due to these organisms would necessarily be more cumbersome. Perhaps in such an instance one would give vancomycin intravenously for the Staph. aureus infection and might give erythromycin or novobiocin in addition in order to be more certain of an antistreptococcal effect.

Cephalothin

Perhaps in the future an agent such as cephalothin, a cephalosporin C derivative, will have special application in cases of polymicrobic bacteremia. Cephalothin is active against certain gram-negative bacteria as well as being active against gram-positive pathogens including penicillin G-resistant staphylococci. It is poorly absorbed from the gastrointestinal tract and for systemic effect must be given intramuscularly. It lacks the basic penicillin structure of 6-aminopenicillanic acid and hence is not cross-allergenic with penicillins.

Continued

Ampicillin

Ampicillin, a semisynthetic penicillin, also may have application in future cases of polymicrobic bacteremia, but it is not active against penicillin G-resistant staphylococci. Ampicillin has recently become commercially available as Polycillin. Ampicillin is active against other gram-positive cocci but less so than penicillin G. Also, it is not effective against as many gram-negative bacilli as is cephalothin.

Murray N. Silverstein, M.D.*
William J. Martin, M.D.*
Robert C. Bahn, M.D.**
Rochester, Minnesota

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*Section of Medicine.
**Section of Experimental and Anatomic Pathology, Mayo Clinic and Mayo Foundation

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Health and Hygiene of the Middle Ages

A medical school in Salerno, Italy, advanced health and hygiene rules. Most captivating is the following poem with its ingenous and disarming frankness. Modern spelling has been used in this instance rather than the old English:

"Great harms have grown and maladies exceeding,
By keeping in a little blast of wind:
So cramps and dropsies, colics have their breeding,
And mazed[1] braines for want of vent behind:
Besides we find in stores worth the reading,
A certain Roman emperor was so kind,
Claudius by name, he made a proclamation,
A scape[2] to be no loss of reputation.
Great suppers do the stomach much offend,
Sup light if quiet you to sleep intend.

Six things that here in order shall ensue,
Against all poisons have a secret power.
Pear, garlick, reddish roots, nuts, rape, and rue,
But garlick chief; for they that it devour,
May drink, and care not who their drink do brew:
May walk in air infected every hour.
Sith[3] garlick then hath powers to save from death,
Bear with it though it make unsavory breath
And scorn not garlick, like to some that think
It only makes men wink, and drink, and stink."*

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*Riesman, David: The Story of Medicine in the Middle Ages, p. 46.
1. Muddled 2. Emission 3. Since

One reason you can't take it with you is that you don't have any left when you go.
—Herbert Prochnow

Advances

Antibacterial Therapy

I. Newer Agents Effective Against Penicillin G-Resistant Staphylococci

Newer Semi-synthetic Penicillins

WILLIAM J. MARTIN, M.D.*
Rochester, Minnesota

THE CORE of the penicillin molecule is known chemically as 6-aminopenicillanic acid;[1] differences among penicillins depend on the nature of side chains attached to the core. It became apparent that the mold that produces penicillin produces the core before attachment of the side chains. Technics were developed which inhibited the attachment of the side chains, thus stopping production of the mold at the point at which only the unattached core had been produced. The fermentation process was scaled up in order to produce 6-aminopenicillanic acid in large quantities, and organic chemists began adding various side chains. Until these data were available, penicillin could be produced only through biologic (fermentation) methods; but with the use of 6-aminopenicillanic acid, the penicillin chemical intermediate produced by fermentation, it became possible to synthesize new penicillins which reflected the variations in the attached side chains. The first commercial example of this ability was the agent phenethicillin potassium produced by N-acylation of alpha-phenoxypropionic acid (the phenyl ester of lactic acid) and 6-aminopenicillanic acid. Further search has led to methicillin, oxacillin, and the other artificial penicillins described below which appear to be only bellwethers of even newer semisynthetic penicillins that have possible clinical application. The agents to be described are currently being investigated because they are active against penicillin G-resistant staphylococci.

Nafcillin[2-4]

After oral administration of nafcillin, serum concentrations of the drug are less than those attained with oxacillin, but nafcillin persists longer in the serum. Nafcillin has recently become commercially available as has uniplu. As has been true of most antimicrobial agents given by oral administration, nafcillin has been absorbed poorly by this route in some persons. Both the free acid of nafcillin and the sodium salt buffered with calcium carbonate appear to be better absorbed on oral administration than the unbuffered sodium salt. The sodium salt of nafcillin buffered with calcium carbonate provides higher serum levels after 30 and 60 minutes, while the free acid gives higher levels at subsequent intervals. Serum levels of nafcillin are higher after oral administration when the subject is in the fasting state and has had repeated doses; it may be thrice increased on simultaneous use of probenecid. After oral administration, peak serum levels of nafcillin are attained within two hours.

Intramuscular

When administered intramuscularly, nafcillin appears to persist longer in serum than methicillin or oxacillin. After intramuscular

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*Section of Medicine, Mayo Clinic and Mayo Foundation.

administration, peak serum levels of nafcillin occur in thirty minutes. Serum binding of nafcillin is less than that with oxacillin but greater than that with methicillin. In addition to inhibiting the growth of penicillin G-resistant staphylococci, nafcillin has a similar effect against certain other gram-positive cocci. It is more active in vitro than methicillin but less active than penicillin G against susceptible organisms.

In the clinical investigation of human adult subjects, the dose of nafcillin by the oral route has varied from 0.25 gm. to 1 gm. given every four hours for as long as ten days. When administered intramuscularly under these circumstances, usually 0.5 gm. has been given every four to six hours. One gram has been given every six hours intramuscularly for as long as seven days. Nafcillin has been given intravenously in daily doses of 3 to 6 gm.

Cloxacillin[4-6]

Like oxacillin and nafcillin, cloxacillin is suitable for oral administration and is active against susceptible gram-positive pathogens, including penicillin G-resistant staphylococci. As is true for oxacillin, strains of Staphylococcus aureus isolated from clinical material and resistant to methicillin showed a corresponding increase in resistance to cloxacillin.[1] Drug-tolerant stains also have been isolated in the laboratory by passage of staphylococci in the presence of cloxacillin. Unlike methicillin, cloxacillin is less effective against a large inoculum than against a small one; this may reflect the fact that it is less resistant than methicillin to staphylococcal penicillinase.[1]

Levels in serum after oral administration of cloxacillin are higher than those following use of oxacillin or nafcillin, but cloxacillin is more rapidly eliminated from the circulation. After oral administration, peak serum levels of cloxacillin are attained in one hour.

Cloxacillin gives better serum antibacterial activity than oxacillin.[5] Serum binding of cloxacillin is similar to that of oxacillin (80 per cent) and hence greater than that of nafcillin. Probenecid inhibits excretion of cloxacillin. Approximately a third of ingested cloxacillin is excreted in the urine six hours after oral administration of the drug.

Intramuscular

On intramuscular administration, cloxacillin, oxacillin, and nafcillin appeared to be equally active when absorption, serum antistaphylococcal activity, and serum binding were all combined in a single assay method.[4] Peak serum levels of cloxacillin after intramuscular administration also occur in approximately one hour.

In the clinical investigation of human adult subjects, the usual dose of cloxacillin by both the oral and the intramuscular route appears to have been 0.5 gm. every four to six hours. While cloxacillin has been effective in various infections due to penicillin G-resistant staphylococci, instances of refractoriness to optimal therapy have been observed, as has been true of methicillin and oxacillin.

Diphenicillin[7-11]

This agent also is absorbed from the gastrointestinal tract and displays in vitro activity against certain gram-positive cocci, including penicillin G-resistant staphylococci. Like that of oxacillin, nafcillin, and cloxacillin, the in vitro activity of diphenicillin is said to exceed that of methicillin against susceptible staphylococci. Variation in inoculum size appears to have no detectable effect on the antibacterial action of diphenicillin.[11] Diphenicillin does not appear to resist the action of penicillinase as well as methicillin does. When probenecid was given with the drug, levels of diphenicillin in blood were described as being higher and more prolonged.[9] Subjects have been noted who failed completely or nearly completely to absorb diphenicillin after oral administration. Otherwise, serum levels of diphenicillin after oral administration are said to compare favorably with those of oxacillin.[8] Diphenicillin is 76 per cent bound in pooled human serum.[7] Like oxacillin, diphenicillin is said not to penetrate well into serous cavities.[11]

In preliminary clinical studies, diphenicillin has given evidence of efficacy. No significant difference in therapeutic efficacy was observed between oxacillin and diphenicillin, and in general the results with diphenicillin were favorable.[11]

In human adult subjects receiving diphenicillin on an investigational basis, 0.5 to 1 gm. has been given by the oral route every four hours. It appears that the 1-gm. dosage was usually given, often in conjunction with probenecid in amounts of 0.5 gm. four times daily. Diphenicillin also has been given by the intramuscular route in comparable dosage.

Comment

There are other semisynthetic penicillins which have reached the stage of preliminary clinical investigation, examples of which are alpha-phenoxypropyl penicillin and phenoxyisobutyl penicillin. Alpha-phenoxypropyl penicillin provides high serum concentration after oral administration but appears to be less active than methicillin against penicillinase-producing staphylococci. Phenoxyisobutyl penicillin appears not to be well absorbed on oral administration and to be associated with a relatively high incidence of gastrointestinal side effects.

It is patently evident that one cannot currently evaluate the precise position of these newer semisynthetic penicillins in the antistaphylococcal armamentarium. The problems of their evaluation undoubtedly will be increased on discovery of still newer derivatives that have possible similar use. However, it is now clear that methicillin is efficacious in the parenteral therapy of some infections caused by penicillin G-resistant staphylococci; and oxacillin, because of its stability in acid, is an effective drug on oral administration in certain infections due to these organisms.

The effectiveness of penicillinase-resistant penicillins depends on at least two properties: (1) the inherent antistaphylococcal potency of the individual drug, and (2) the degree to which it resists the effects of penicillinase. The ultimate clinical potential of a given drug will be influenced by multiple factors, of which these two properties, while important, probably represent only initial considerations.

Analysis of the laboratory and clinical findings available to date does not immediately suggest that any of the newer compounds that are designed for antistaphylococcal use possess clear-cut superiority over methicillin and oxacillin. However, since nafcillin can be given both orally and parenterally it does have the virtue of unity. Significant differences in the clinical application of these drugs and of similar ones to follow will be evident only after their continued investigation.

Cephalothin

Cephalothin,[4,12] a cephalosporin C derivative, is active against certain gram-positive cocci, including staphylococci, that are resistant to penicillin G. In addition, it is active against certain gram-negative bacteria, including coli-aerogenes, Proteus, and Klebsiella organisms. Because of its relatively wide spectrum of activity, it has been suggested that cephalothin might have special application in possibly mixed infections. Cephalothin is poorly absorbed from the gastrointestinal tract.

Cephalosporium sp. gives rise to several antibiotics, including cephalosporin C.[13] By chemical removal and replacement of the aminoadipic acid side chain of cephalosporin C, penicillinase-resistant compounds which are 100 times as active as the parent compound and other new cephalosporins with wide antibacterial spectra have been produced. Cephalothin appears to be but a bellwether of a series of semisynthetic compounds which may rival the penicillin derivatives.

Organisms Affected

The in vitro activity of cephalothin against susceptible gram-positive pathogens is similar to that of oxacillin. It is bactericidal against susceptible gram-positive cocci and gram-negative bacilli in concentrations only slightly greater than those required for inhibition. Following intramuscular administration of cephalothin and methicillin, they appeared to be equally active when absorption, serum antistaphylococcal activity, and serum binding were combined in a single assay method.[4] Serum binding of cephalothin

Continued

release for hostility?

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Side effects (chiefly nervousness and insomnia) are infrequent, and usually mild and transitory. *Cautions:* 'Eskatrol' *Spansule* capsules should be used with caution in the presence of severe hypertension, advanced cardiovascular disease, or extreme excitability. There is a possibility, though little likelihood, of blood or liver toxicity or neuromuscular reactions (extrapyramidal symptoms) from the phenothiazine component in 'Eskatrol' *Spansule* capsules.

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is greater than that with methicillin, but less than that with oxacillin. After intramuscular injection, peak serum levels of cephalothin are attained in about thirty minutes, and detectable levels are present at the end of four hours. In the first six hours after its intramuscular injection, 70 per cent of the dose is recoverable in the urine.

In preliminary clinical trials cephalothin has given encouraging results. It has been administered to human subjects in amounts of 0.5 to 1 gm. every four to six hours by the intramuscular route for more than eight weeks. Staphylococcal bacteremia, pneumonia, and osteomyelitis have responded to cephalothin. Pneumococcal pneumonia is susceptible to the drug, and cephalothin may have application in this condition in patients who are allergic to penicillin.

Route of Administration

When intravenous therapy has appeared mandatory, a total daily dose of 2 to 6 gm. has been given. When intermittent administration is desired, 0.5 to 1 gm. in 10 ml. of normal saline is injected over three or four minutes, either directly or through tubing when the patient is receiving other fluids parenterally. Continuous infusion in 5 per cent dextrose in distilled water or normal saline can be used. If intravenous doses are in excess of 6 gm. daily, thrombophlebitis commonly occurs. On intramuscular administration of the drug, pain at the site of injection may necessitate addition of 2 per cent procaine to the solution. Cross-allergy with other antibiotics has not been reported. Urticaria, eosinophilia, neutropenia, increased serum glutamic oxalacetic transaminase activity, and increased azotemia have been noted.

Comment

Cephalothin may possess an advantage of considerable clinical potential: Lacking the basic penicillin structure of 6-aminopenicillanic acid, it may not have cross-allergenicity with the penicillins. The nucleus of cephalothin is 7-aminocephalosporanic acid.

Cephalosporin derivatives, while resistant to staphylococcal penicillinase, are reported as being degraded by cephalosporinases present in certain enterobacilli. If such enzymes are productive of future clinical problems, such as contributing to bacterial resistance, there is the possibility of synthesizing cephalosporinase-resistant cephalosporins.[14]

Sodium Fusidate (Fucidin)

The soduim salt of fusidic acid[15-20] is an orally administered antibiotic, the antibacterial spectrum of which includes penicillinase-producing strains of Staph. aureus. It has the cyclopentenophenanthrene nucleus but is said not to show hormonal activity. There is some evidence that conjoint administration of sodium fusidate and penicillin produces an enhanced effect against certain organisms including penicillin G-resistant strains of staphylococci.[20] Because of this enhanced effectiveness, it has been recommended that fusidic acid and penicillin G or a penicillinase-resistant penicillin be given concurrently. It is theorized that fusidic acid reduces the population of penicillinase-producing bacteria while the concomitantly administered penicillin eliminates those which show active growth. Synergistic activity with erythromycin and novobiocin also has been described.

Organisms Affected

Sodium fusidate is active mainly against gram-positive micro-organisms and Neisseria; it is relatively inactive against gram-negative bacilli and fungi. It has some activity against Mycobacterium tuberculosis. The antistaphylococcal effect of sodium fusidate is most pronounced against a small inoculum. Staphylococcal resistance to the drug develops rapidly in vitro; in addition, staphylococci resistant to the drug have been obtained from patients treated with this agent. The in vitro activity of the antibiotic is considerably decreased in the presence of serum; the effect of the serum appears to represent a reversible binding to proteins.

Route of Administration

Serum concentrations of sodium fusidate are at a peak in two hours after an oral dose of 500 mg., and detectable amounts may be present forty-eight hours thereafter. Conjoint administration of milk may so delay absorption of sodium fusidate that peak con-

Continued

centrations do not occur for four to eight hours. There are considerable individual variations in the serum levels obtained. The drug is said to diffuse readily into body tissues and fluids. Concentrations in bile are five to twelve times as high as levels in serum. Less than 1 per cent of the ingested dose is excreted in the urine.

Oral doses of 250 to 500 mg. have been administered to patients two to four times daily, but the usual dose appears to be 500 mg. given thrice daily. Some patients have received the drug for as long as twelve weeks.

Undesirable Reactions

Untoward reactions to sodium fusidate have included skin reactions and gastrointestinal disturbances including nausea, vomiting, and diarrhea. The question has been raised whether the drug has proved aggravating to peptic ulcers. Both in experimental animals and in human subjects, hepatic dysfunction, as manifested by increased retention of sulfobromophthalein in the serum, appears to have followed use of the drug. Neutrophilia on administration of sodium fusidate has been noted in experimental animals. A catabolic or perhaps an antianabolic effect manifested by increased urinary output of nitrogen, potassium, phosphorus, and possibly sodium has been noted in patients receiving the drug.

Comment

Sodium fusidate appears to have demonstrated antistaphylococcal effect in patients, some of whom had serious infections including bacteremia. However, the rapidity with which staphylococci have developed resistance to the agent may be ominous. The possibility that conjoint administration of penicillin has an enhanced effect, even against penicillin-resistant staphylococci, is at least interesting. Doubt has been expressed that fusidic acid will prove to be a major antistaphylococcal antibiotic, but in view of several of its characteristics, including its ability to depress the production of penicillinase by staphylococci, it may prove to be a valuable "research tool."

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10-20 may be obtained from author.

Victory

He who gains a victory over other men is strong; but he who gains a victory over himself is all powerful.—Lao-tse

Industrial Medicine

Emotional Problems in Trauma*

Much can be learned about the emotional problems of the industrially-injured if time is taken to observe him; for a person's emotional injury, however minor, cannot be completely separated from his psyche. His thoughts about the cause and consequences of his physical injury, his feelings and expressions concerning them, and his solutions to these problems are as much a part of him as the trauma producing them.

On Giving Advice

Nothing is so badly needed, so freely given, and so frequently ignored as advice. The best kind of advice is the advice you buy, because that is the advice most apt to be used. Free advice is often worth no more than what is paid for it, and bad advice costs nothing until you use it. It has been said that one should ignore half of the advice he is given and give only half of the advice he is tempted to give. The trick in each case is in knowing which half.

Causation of Accidents

Tremendous efforts by the safety movement have been responsible for the application of safety devices, safeguards, and safe procedures in the operation of machines and other equipment. The marked reduction in the accident-frequency rates attests to the success of these efforts. Yet accidents still occur.

Emotions

No less an authority than Dr. Will Menninger[1] has recently written that at least 75% of accidents have a major psychological component in their causation. A case in point is represented by the patient who sustained a bilateral fracture of the os calcis and a fracture of the right ankle, after having been knocked off the top of a furnace by the "C" hook of a crane, falling about 20 feet and landing on his heels. Discussion with the patient revealed a number of contributing emotional factors. He was concerned about his 12-year-old son who would be at home alone at lunch time and would have to prepare his own meal, because the alcoholic wife and mother had not returned home from her usual weekend binge. Further complicating the emotional picture was the fact that the crane operator had been ordered out of his cab about 30 minutes earlier and reprimanded severely for having damaged a furnace through carelessness due to heavy drinking over the weekend. When the injured employee had absently walked to the front of the furnace for no apparent reason, the crane operator was obviously less than fully attentive, as he was absorbed in venting his anger on the foreman who had "chewed him out" in the presence of fellow-employees. Such were the features coloring and complicating the emotional framework within which the accident occurred.

Accident Proneness

This is a term which has had a strong play, but MacIver[2] suggests substituting the term "accident susceptibility," because this takes into account all of the factors which tend to predispose an individual to accidents. Many accidents do occur when an individual is emotionally upset; yet being upset at one time or another is an inevitable consequence of living. The answer then is not to stop being upset, but to educate people to be on the alert when under unusual stress, even withdrawing from the accident potential if possible. Because an individual has two or three accidents in a given period of time is no reason to assume he had these accidents because he was emotionally disturbed. He may have been "accident susceptible." The particular

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*Second Symposium on Disabilities 9-20-63.

circumstances producing this susceptibility may have lasted only a short period of time, and it may be two or three years before he again goes through a susceptible period.

Emotional Response to Accidents

The emotional response in patients will range from no noticeable effect on recovery to frank post-traumatic neurosis. The latter may be an exceedingly difficult condition to cope with if it is not recognized early.

Educated guesses place the number of persons having a measurable amount of emotional residual following injury at one to two percent, or roughly 3,500,000 persons. Generally speaking, these residuals occur more frequently when the trauma is a life-threatening situation. In the early period after the accident the physician should utilize fully the power of suggestion through a supportive, encouraging, and sympathetic approach; later, a combination of encouragement and warmth, with firmness but without punitiveness, will minimize the chances of residual emotional findings.

Patients sustaining similar trauma often react quite differently. An example occurred in two individuals who sustained amputation of a thumb. In one instance the level of anxiety and emotional instability was overcome and a successful recovery was made. The other case was entirely different, and psychiatric consultation which was sought after six months failed to be of any assistance. It remains to be seen what will occur following the conclusion of litigation brought by the patient. Prognosis is poor, to say the least. But no one can gainsay what might have happened with psychiatric treatment on the first day.

Summary

Emotions may be a causative factor in the occurrence of accidents, as well as a factor in the individual's response to the trauma sustained. Accident-susceptibility, rather than accident-proneness, is a better term to describe the personal and environmental factors responsible for the movement of individuals into and out of periods of frequent accidents. Education for alertness in times of stress, even to the point of withdrawal from known accident potential, is often needed.

Most individuals weather the emotional problems of trauma very well. But at times it may be more important to treat the psyche than to concentrate on the trauma repair. The psychiatrist can be of inestimable help to the sympathetic, yet firm, attending physician in recognizing and treating the difficult post-traumatic neuroses. Most individuals can be returned to full occupational capacity.

Merle Bundy, M.D.
Pittsburgh, Pennsylvania

Great occasions do not make heroes or cowards; they simply unveil them to the eyes of men. Silently and imperceptibly, as we wake or sleep, we grow strong or weak; and at last some crisis shows us what we have become.—Cannon Westcott

It aint no disgrace for a man to fall, but to lie there and grunt is.—Josh Billings

A man who cannot lead and will not follow, invariably obstructs.—The Pick-Up

Grand Rounds

Subacute Diffuse Thyroiditis

Formerly, subacute diffuse thyroiditis was considered a rare disease; however, clinicians are now making the diagnosis much more often than during the first thirty years of this century. It is difficult to determine if this increase in cases of subacute thyroiditis is due to a higher incidence of the disease or to a better knowledge of the clinical picture and the abnormalities detectable with newer laboratory tests now available. However, the statement of Cochran and Nowak, "It is no exaggeration to say that thyroiditis as an entity is unknown to the average internist and surgeon," is not true today.[1]

Subacute diffuse thyroiditis was described by De Quervain in 1904, and since then has received various names, among them De Quervain's thyroiditis, pseudotuberculous thyroiditis, granulomatous thyroiditis, and giant cell thyroiditis.[2]

Incidence

In Table 1 several reports regarding the incidence of suppurative thyroiditis reveal very clearly in chronological order how the incidence of the disease decreased from 94 percent in 1928 to one percent in 1942.[3]

The incidence of subacute diffuse thyroiditis in relation to diseases of the thyroid gland was put by Means at approximately one percent.[4] At Duke Hospital, from 1930 to 1949, 2,685 cases of thyroid disease were admitted, and among them were 36 cases of subacute thyroiditis,, an incidence of 1.3 percent.[5] At the Cleveland Clinic, from 1936 to 1947, a diagnosis of disease of the thyroid gland was made in 7,045 cases, and of these 93 were subacute thyroiditis, an incidence of 1.3 percent.[3]

Etiology

The multiplicity of synonyms, the disputes as to etiology, and the many and different therapeutic approaches to De Quervain thyroiditis reveal how little is really known about this disease.

Continued

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*Presented as a Medical Grand Rounds at Mt. Sinai Hospital, Minneapolis, October 8, 1963.

TABLE 1*

Author	Year	Total Acute	Suppuration	Per-cent
Robertson	1911	96	40	42
Hagenbuch	1921	43	30	70
Burhans	1928	67	63	94
Cochrane and Nowak	1934	10	3	30
Means	1937	12	2	16
McQuillan	1938	17	6	35
Sallick	1942	12	1	8

*From Osmond and Portmann[3]

Virus

That the agent of the disease could be a virus has been suspected for many years. The clinical picture, the absence of suppuration, the fact that sometimes the disease is preceded by an upper respiratory infection, and the apparent self-limiting course of the disease, seem consistent with a viral agent. It is the opinion of the supporter of this theory that the virus infects the gland and damages the cell lining of the follicles. Then colloid escapes into the tissue spaces and provokes a foreign body reaction which attracts cells that phagocytize the colloid.[6]

In 1957 Eyland and Zmucky published an article[7] presenting very interesting data in support of the viral origin of subacute thyroiditis. They made complement-fixation tests for mumps virus in 11 patients with subacute thyroiditis, and found that 10 of the 11 cases gave positive results. They used as controls 52 healthy women aged 30-64 years. The results were as follows: 42 were negative, six were positive in a titer of 1/10, and four were positive in a titer of 1/20. The lowest titer in the patients with subacute thyroiditis was 1/40, and the range went up to 1/160. In addition, in two of the 11 patients a virus was isolated from the biopsy specimen of the thyroid gland which was thought to be identical with the mumps virus. The biopsies were diagnostic for De Quervain thyroiditis.

Infectious Agent

In January of 1962, Swann[8] reported twelve cases of acute thyroiditis from the same urban community, seen and treated between March and June of 1961: twelve males and nine females. No familial occurrence was noted. Steroid therapy was used to treat all the patients, and they responded well to the treatment within approximately ten days. This report suggests an infectious agent.

Autoimmunization

The other hypothesis is one that includes De Quervain thyroiditis among the autoimmune diseases. The lack of common occurrence of subacute thyroiditis in association with mumps in the child or adult, and the absence of reports identifying the virus or revealing positive complement-fixation to it, are believed to be counter-arguments against the viral etiology.[9] In 1956 Roitt, Doniach, Campbell and Hudson demonstrated a precipitin type antibody reacting with thyroglobulin in the sera of patients with Hashimoto's disease, and proposed the theory of autoimmunization in the etiology of this disease.[10] Witebsky et al. extended this concept of autoimmunization, that is, sensitization of the patient against his own thyroid, to include acute granulomatous thyroiditis.[11,12]

In 1958 Felix-Davies reported a case of subacute diffuse thyroiditis in which precipitin antibodies to thyroglobulin were demonstrated, suggesting that the thyroglobulin-bound antigen was implicated in the disorder.[13] Roitt and Doniach reported in the same year the result of thyroid antibody studies in 19 patients with subacute thyroiditis. Thyroid antibodies were demonstrated in 13 (68%) of the patients.[14] Balfour et al. in 1961 did studies with fluorescent antibody in patients with all types of thyroiditis, trying to find autoantibodies to an antigen in thyroid colloid distinct from thyroglobulin. They had three cases of De Quervain thyroiditis, and one (diagnosis proved by biopsy) was positive.[15] Witebsky and Rose had 20 cases of De Quervain thyroiditis, and in seven of them the tanned-cell hemagglutination test was positive, an incidence of 35 per cent. The diagnosis in these cases was confirmed by biopsy. Table 2 is a partial reproduction from the above mentioned authors.[16]

The presence of antibodies against the thyroid within the same body is undeniable; but it may be that the rise in antibody titer to thyroglobulin is a phenomenon secondary to liberation of the thyroglobulin outside the gland after thyroiditis has begun.

The viral and the autoimmunological theories can be reconciled. When attempts were made to provoke autoimmune thyroiditis, Hashimoto's disease, in the rabbit, the antigen alone was unable to produce the disease. It was not until Freund's adjuvant was added to the antigen that Hashimoto's disease was produced.[18]

TABLE 2*

Tanned-Cell Hemagglutination Test in Different Kinds of Thyroiditis

Thyroiditis	Negative	1/10	10/100	100/1000	1000/1000	10000+	Tot.	Pos.	%
Hashimoto's disease	22	0	3	1	6	0	32	10	31
Chronic nonspecific	23	10	10	20	24	8	95	72	76
Riedel's struma	3	0	1	1	1	0	6	3	50
De Quervain type	13	1	2	2	2	0	20	7	35
Acute thyroiditis	6	0	1	1	0	0	8	2	25

*Partial reproduction from Witebsky et al.[16]

Pathology

Gross Pathology

The thyroid is usually enlarged to twice or more its normal size. Both lobes may be affected, but sometimes only a portion of one is involved. Some degree of perithyroiditis is frequent, and occasionally edema of the cervical muscles and loose adhesions to the trachea are present. The areas affected in the gland are firm and yellowish-white.

Microscopic Pathology

The microscopic changes are highly variable in extent and type. There is degeneration of follicles, infiltration of leukocytes, lymphocytes, and plasma cells. The characteristic lesion is the granuloma composed of a central mass of colloid with a margin of giant cells and mononuclear cells.

Continued

The giant cell formation often appears to be a reaction to altered colloid, and some giant cells seem to be formed by fusion of follicular cells around colloid masses. Some degree of fibrosis and more rarely fibroblastic activity in the gland and in the gland capsule may be seen.[18,19,20]

Clinical Picture

Reviewing a part of the literature, we have collected and pooled 57 cases of subacute nonsuppurative thyroiditis to which we have added a new case reported in detail in this paper.[21-34] The description of the clinical picture will be based on these 58 cases.

Age and Sex

In these 58 patients there was a preponderance of females in a proportion of 4.8:1 (See Table 3).

TABLE 3
Age Distribution, 58 Patients (48 Females, 10 Males)

Age	Cases	Percent
10-20	1	1.7
20-30	5	8.6
30-40	18	31.0
40-50	24	41.4
50-60	8	13.8
60-70	2	3.5

Physical Findings

The onset of the disease can be acute with very severe symptoms, subacute, or mild. In general, the main complaint is tenderness in the region of the neck, radiating characteristically to the submaxillar area up to the ear. Because this pain is worse when swallowing, the patients often complain of "sore throat." Accompanying this tenderness in the neck there may be fever, weakness, malaise, tachycardia, nervousness, tremor, and loss of weight.

The thyroid is enlarged, firm, tender, and usually the entire gland is involved, although the enlargement may be limited to one lobe.

Course of the Disease

De Quervains thyroiditis is a self-limiting disease that usually runs its course in four to eight weeks. Rarely, a goiter is a late residual of the disease.

Some authors[35] distinguish by clinical observation and laboratory findings four phases of the disease: (1) thyrotoxic phase, (2) euthyroid phase, which can pass unnoticed, (3) hypothyroid phase, and (4) recovery phase.

The incidence of symptoms and physical findings in the 58 patients in this review are presented in Table 4.

Correlation of Pathologic and Physiologic Changes

Thyrotoxic Phase

The acute pathological changes in the thyroid gland are characterized by congestion and marked edema,, and such changes progress quickly to necrosis of the epithelium of the thyroid follicle. Very soon the body is flooded with thyroid hormone, and the damaged or destroyed cells cannot concentrate iodine or continue producing hormone.

TABLE 4
Symptoms and Physical Findings in 58 Cases of Subacute Thyroiditis

Symptoms	Cases	%
Thyroid pain	58	100
Fever	40	69
Sore throat	37	64
Weakness	35	61
Physical Findings	**Cases**	**%**
Thyroid Enlargement	57	98
a) entire gland	42	72
b) one lobe	15	26
Thyroid tenderness	58	100
Tachycardia	22	38

Euthyroid Phase

The phagocytic response begins with infiltration of histiocytes and giant cell formation, giving the characteristic lesion of a granuloma composed of a mass of colloid with a margin of giant cells and mononuclear cells.

Hypothyroid Phase

Clinically the patient passes from an acute thyrotoxic phase through a short euthyroid stage to a hypothyroid stage, if the necrosis in the gland has been severe and extensive. Even in the severe stage of the granulomatous phase it is possible to see regeneration of the follicles, and this regeneration is a prominent feature during recovery.

Recovery Phase

The rate at which the regeneration of the follicles takes place is variable, as is the clinical picture of the disease. However, recovery seems to be complete, although fibrosis may be present in the gland among normal appearing tissue.[35]

Laboratory Findings and Thyroid Function Tests

Some observers[36] report a significant degree of anemia in patients with subacute thyroiditis, but normal hemoglobin or very mild anemia was present in our patients. The leukocyte count ranged from 4,200 to 18,160 with a mean value for 27 patients of 9,110 with 68 percent polymorphonuclear cells. The sedimentation rate was within normal limits in only two patients, while in the others it ranged from 31 to 122 mm/hr. with a mean value in 27 cases of 65 mm/hr.

Basal Metabolic Rate

The basal metabolic rate in nine patients ranged from −12 to +25% with a mean value of +6%. The protein-bound iodine in nine patients was

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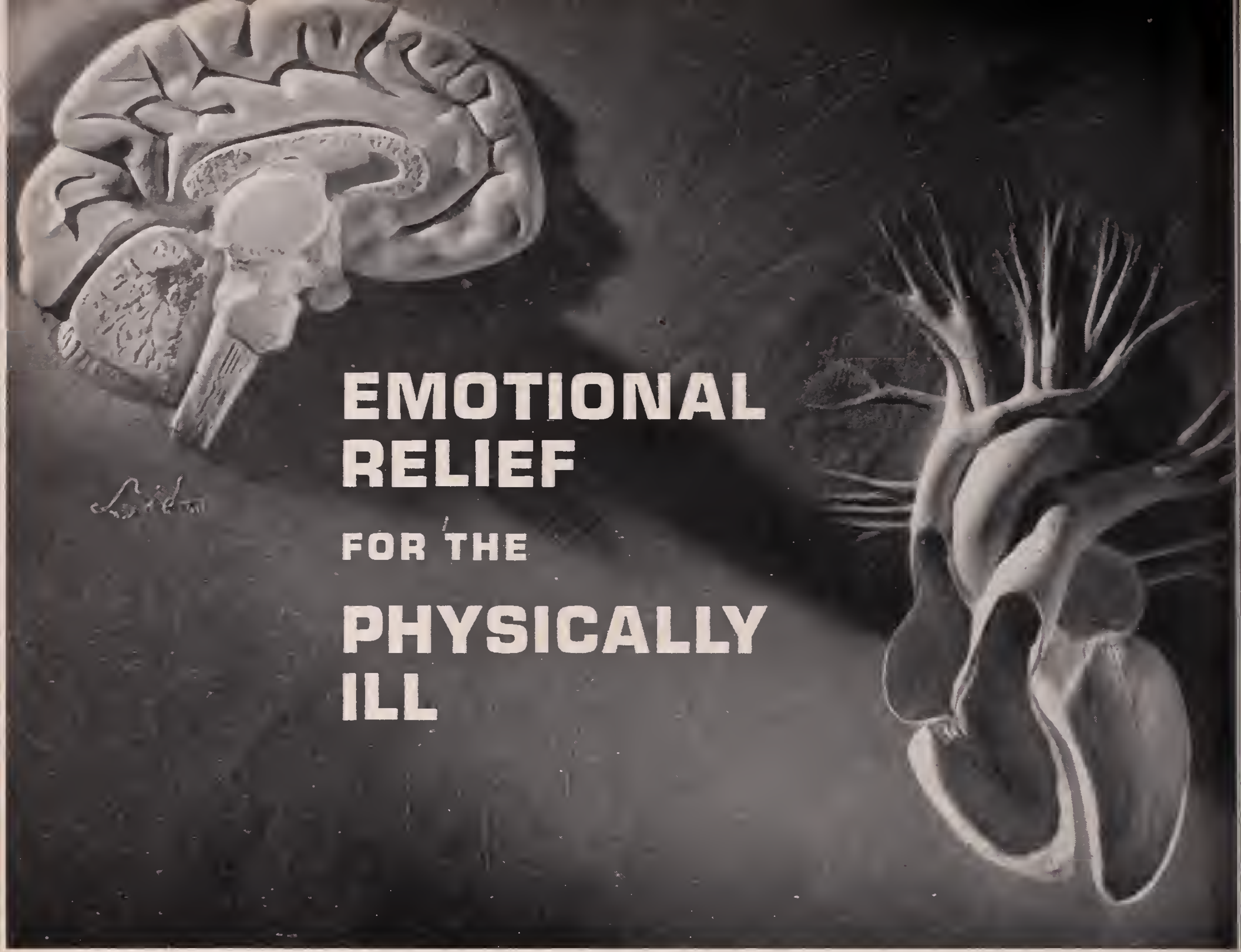

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4.2 to 12.2 micrograms % with a mean value of 8.8 micrograms percent. The thyroid I^{131} uptake in 20 patients ranged from 0 to 35% in 24 hours with a mean value of 7.7% in 24 hours.

Thyroid Stimulating Hormone

In three patients a thyroid stimulating hormone test for stimulation of the thyroid during the acute stage was done. The results in these patients and in 12 others reported by Skillern, Nelson and Crile show that the increase in thyroid uptake with thyroid-stimulating hormone stimulation was negligible in all but two patients.

Plasma Protein

In six patients reported by Skillern et al.[36] the electrophoretic analysis of plasma protein was normal except for a moderate decrease in serum albumin in five, a slight increase in gamma globulin in two, an increase in alpha 1 and 2 globulin in one, and a slight elevation of beta globulin in one.

Diagnosis

When the subacute diffuse thyroiditis presents the classical symptoms of thyroid pain, with enlargement of the gland and tenderness along with fever, sore throat, and tachycardia, the diagnosis is not difficult. The physician should be careful to palpate the thyroid in patients with complaint of sore throat or submaxillar or ear pain, to avoid the mistake of

TABLE 5

Laboratory Findings and Thyroid Function Tests in 27 Patents with Subacute Thyroiditis

Reference	Case	Leukocyte Count	Polymorpho-nuclear Cells (%)	Sed. Rate (mm/hr.)	RIU %/24 hr.	Serum PBI (Micro-gm.%)	BMR (%)
21	1	14,700	77	46	0	13.3	
	2	9,000		52	2	8.4	
22	18	4,200		38	12	7.5	−7
23	20	4,800	74	98	0		+15
	21	18,160	76	74	13		+18
	22	9,100	33	49	7		+12
	23	8,200	54	105	0		+25
	25	13,500	71	122	2		−9
	26	14,600	71	105	7		−1
	34*	6,600	62	31	35	4.2	−12
24	M. F.	9,850	77	82			
	I. F.	9,000	58	61	5		
	H. G.	10,250	66	20			
	D. T.	8,500	67	50			
	E. W.	10,450	69	101	5		
	G. Z.	7,600	82	65	2		
	J. K.	7,950	68	24	15	6.7	
	E. K.	8,750	60	43	11		
	L. C.	7,350	63	106		8.8	
	E. C.	10,400	74	65	1	8.8	+15
	R. F.	6,300	70	111	1	12.2	
	R. C.	11,700	86	57	1	9.8	
	N. H.	8,900	77	29	11		
	M. M.	8,800	66	30	24		
	Mean	9,110	68	65	7.7	8.8	+6

*Case reported in this paper

Continued

treating a subacute thyroiditis as a pharyngitis, otitis, or neuralgia. The help of the laboratory is very important, and a low thyroid I^{131} uptake, a high or upper normal protein-bound iodine and a high sedimentation rate in the presence of symptoms, even mild ones, are characteristic of the disease. If there is doubt about the diagnosis, the use of needle biopsy[37] either with a Silverman or Menghini needle may be advisable.

Treatment

It is difficult to assess the effectiveness of therapy in a disease which presents so much variation in its self-limiting clinical course.

X-Ray Therapy

X-ray therapy to the thyroid gland has been reported to be successful[3] but has the disadvantage of seven to 14 days' delay before relief of symptoms, a relatively high rate of relapse, and post-recovery hypothyroidism.

Antithyroid Drugs

Some authors have reported the use of antithyroid drugs (propylthiouracil) with good results.[6,29,38] At the present the most effective drugs for the relief of symptoms in subacute thyroiditis are cortisone and ACTH.[21,23,25,27,28,31,32] Recently, Higgins, Bayley and Diosy reported good results in the treatment of subacute thyroiditis by the suppression of endogenous thyroid-stimulating hormone with the use of L-triiodothyronine.[39]

Cortisone Medication

In general 250 mg. of cortisone or 40 mg. of prednisolone is the initial dosage, later decreasing to lower maintenance dosage. Maintenance dosage and length of therapy must be determined in each individual case, since relapses with reduction of dosage or cessation of treatment are common. The recurrence of the symptoms after stopping the drug does not indicate that the treatment has failed, since treatment may again be resumed with disappearance of symptoms.

Steroids are not a curative treatment, and the action of these drugs is for relief of the symptoms, which is accomplished within 12 to 48 hours after beginning the treatment. The duration of the disease is probably not altered, although signs and symptoms are suppressed.

Case Report

A 34-year-old white female was admitted to Mt. Sinai Hospital on 7-21-63 with the chief complaints of nervousness, loss of appetite, six-pound weight loss, and tremor for two weeks. She also complained of stiffness and tenderness of right side of neck for three to four days. During the two weeks prior to admission she had been feeling restless, hyperactive, unable to sleep and found it difficult to concentrate. She had been perspiring very heavily and her appetite became poor. One week prior to admission she had a "dizzy spell" with palpitations, nausea and vomiting. Since then she had had episodes of palpitations with shortness of breath, pain in her right shoulder, right elbow and back of left leg. Four days prior to admission she noticed tenderness and stiffness of right side of her neck with swelling.

Past History

The patient had been nervous most of her life, but she had been getting worse during the past year. Dilatation and curettage in October, 1962, for menorrhagia and metrorrhagia; tonsillectomy in childhood. She denied any recent upper respiratory infection. Family history was noncontributory.

Physical Findings

B.P. 130/84, T. 98.6, P. 84, R. 20. She was alert and co-operative, and hyperactive with frequent and quick movements and rapid speech. Nystagmus was present in lateral gaze. The thyroid was enlarged, mostly in the right lobe with marked tenderness to palpation. No adenopathy was present. Breasts and axillae were negative. Lungs were clear. Heart rhythm was regular, heart sounds distant, and no murmers were present. The abdomen was soft; liver, spleen and kidneys were not palpable; there were no masses or tenderness. There was a fine tremor of the hands. The skin was moist. Neurological examination was essentially negative. Rectal and pelvic examinations were negative.

Laboratory Studies

Chest X ray: old punctate calcification within left upper lung field and in left apical area.

Hg. 12.5 gm. Leukocytes 6,600, PMN 62%, Lympho. 31%, Mono. 4%, Eosin. 1%, and Basoph. 2%. BMR —12%, EKG normal, BUN 10 mg%, glucose 90 mg%. Total proteins 7 gm. per 100 cc., albumin 4.2 gm% and globulin 2.8 gm%. Cholesterol 234 mg%. Ceph. floc. negative.

Urinalysis: sp. gravity 1.017, H 5, WBC/hpf 8-10, many epithelial cells. Crystals: Ca oxalate, few. Mucous threads. VDRL negative. PBI 4.2 mcg. Sed. rate 31 mm. Antithyroid precipitation test negative. Thyroid I^{131} uptake 35% at 24 hours.

The course in the hospital was uneventful. The patient was afebrile, received no medications, and was discharged improved on the sixth hospital day.

Although the thyroid I^{131} uptake was normal, a diagnosis of subacute diffuse thyroiditis was made on clinical grounds.

R. A. Guerrero, M.D.
Mt. Sinai Hospital

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13-39 Can be obtained from Grand Rounds Editor at Mt. Sinai Hospital.

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—Wall Street Journal

When you come to the end of your rope, tie a knot in it and hang on.—Papyrus

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Abstracts, Briefs and Commentaries

STATUS OF MEDICAL PRACTICE IN ENGLAND

In England the migration of doctors is of great national concern. Approximately 4,000 doctors are employed in British hospitals. Many of these are graduates of Asia and Africa where they can ill afford to train them properly for export, and where the doctor supply is inadequate.

A survey shows that 9.5 percent of the graduates from Birmingham medical schools migrate to the United States, Canada, New Zealand, Australia, or to developing countries. Not included in the emigration estimate are those doctors who join the military or air force. Davidson in his report computed that more than 300 doctors were exported annually from Great Britain to North America. The Platt committee estimated that of the 1700 medical graduates produced annually, approximately 140 of them may be expected to migrate out of the country within a period of 15 years. The shortage of doctors because of this migration is causing ever greater concern.

It is estimated that it costs 10,000 pounds to educate one doctor, and this cost is largely borne by the state. When a doctor migrates out of the country the state loses both the doctor and the cost of his education. The reasons for this emigration are enumerated as being dissatisfaction with medical health service, change to a better climate, the desire to travel, the overcrowded conditions in England, better opportunities elsewhere, marriage, missionary service, and the opportunity for general practitioners to work in hospitals where they can do some surgery instead of being required to refer it to the hospital where it is done by hospital surgeons.

An extensive symposium was held at Oxford on the loss of incentives in general practice. This symposium was attended by representatives of the National Health Service, doctors, and educators. It was pointed out that there was a considerable amount of "malaise" in general practice, and that five percent of the practitioners were practicing the poorest standards of medicine. These were referred to as the "dead wood" or the "half dead" who lost interest in their practice long before they were due to retire.

It was pointed out that the expense of operating a general practice is so high that many are obligated to remain poorly equipped for proper

Continued

examination and diagnosis, and they are so busy with "long patient lists" that they have no time to read or study. Because the physician's service is free, the "system" develops into a group of patients who have little or nothing wrong with them. In order to improve this waste of the physician's time and effort, it was suggested that those with minor complaints be referred to a nurse or pharmacist. It was also suggested that several of the general practitioners join to form groups in order to be able to afford better facilities.

The general practitioner was also offered a bonus for early diagnosis of diabetes or cancer, but this was largely eliminated because of the increased expense to the state.

To improve the education and qualifications of the general practitioner, it was suggested that he be permitted to observe and study the care of his patient when admitted to the hospital.

A short vacation was also suggested in order that the general practitioner might visit clinics or take short courses in a medical school or hospital.

Comments: During World War I I served as an American doctor attached to British Forces, in front line aid posts, casualty clearing stations, and base hospitals. I met many British doctors for whom I developed a deep respect because of their bravery under combat conditions, their fund of knowledge in their profession, and their skill.

British medical literature I read with pleasure, both for the wonderful command of the English language and the excellence of their reviews of medicine and its advances. When I read about the emigration of the general practitioner and the decline of his status, as they now exist, I was amazed, for I had enjoyed the personal experience of having been entertained at dinner by a fine London family who suggested that they would call the panel physician for a night-time emergency, but if they were required to enter a hospital for a medical or surgical emergency, they would without reservation employ their private medical doctor or surgeon.

If we value the high standards of our own general practitioners both professionally and economically, all doctors must think seriously about anything that might cause a change to that which is now obvious in England. Could the deterioration of the general practitioner in England be the result of the National Health Service regulations and of the lack of healthy competition? I am certain that many American doctors would migrate if they were underpaid, overworked, and subjected to the same rules and regulations which have been enforced in England. Our general practitioners are to be complimented on the formation of their own American board.

Stanley R. Maxeiner, Sr.
Minneapolis, Minn.

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4. Medical World Conference—A Conference on General Practice. Lancet—October 26, 1963, p. 878.

VERTIGO

Vertigo implies a hallucination of movement, accompanied by a reflex tendency to counteract this movement, which may result in loss of equilibrium. Anything outside this, such as faintness, syncope or nausea, cannot be accepted as synonyms for vertigo.

When confronted by a patient with vertigo, it is important to exclude disorders in the central nervous system. Anyone who loses consciousness during a vertiginous attack should be suspected of having epilepsy. Vertigo occurs as an aura in about 16 percent of epileptics. It may also be the first and even the only sign of multiple sclerosis.

When an intracranial blood vessel ruptures or becomes thrombosed, sudden vertigo may be an early feature but is soon overshadowed by more serious symptoms. When the anterior and posterior inferior cerebellar arteries are thrombosed, the syndrome produced by involvement of the brain stem and cerebellum includes vertigo, with deafness and tinnitus.

Tumors of the posterior cranial fossa may give rise to marked and persistent vertigo as the only symptom for a time; but acoustic neurinoma, which is far the commonest of such tumors, rarely has vertigo as a prominent feature. In children the possibility of a cerebellar glioma should be borne in mind.

Peripheral causes of vertigo include damage to the end organs or the peripheral vestibular neuron. In these cases spontaneous nystagmus seldom lasts more than a few weeks. Endolymphatic hydrops (Ménière's disease) is much the commonest peripheral cause of vertigo. Vascular spasm affecting the labyrinth is the primary factor. The most characteristic manifestation is a sudden attack of vertigo lasting from a few minutes to two hours, often heralded by tinnitus and fullness in the ear on the affected side.

Infection of the middle ear may erode the bony labyrinth and cause vertigo. Other forms of infective vertigo include the neurolabyrinthitis of meningococcal meningitis, which is bilateral, and mumps, which frequently affects only one ear.

Streptomycin and dihydrostreptomycin are recognized as having vestibulotoxic side effects. Kanamycin and neomycin also affect the ear. In the University Hospitals streptomycin is given only to patients who cannot be helped by other means.

The spontaneous phenomena of vestibular disease consist of vertigo, nystagmus and ataxia; the induced phenomena chiefly consist of abnormalities of the reflex responses to stimulation of the vestibular end organs. Abnormal responses to caloric and positional tests are seen in about 90 percent of cases of Ménière's disease. In cases of tumor of the seventh cranial nerve and vestibular neuronitis the incidence of abnormal responses comes close to 100 percent. In all these cases the after-nystagmus lasts longer in one direction than in the other. In lesions of the eighth cranial nerve or labyrinth there is a difference in sensitivity between the two vestibular systems, manifested by a shorter duration of the after-nystagmus following syringing with cold and warm water.

Whether the otolith system is affected peripherally or in its central connections, the occurrence of positional nystagmus is important. It may be the only physical sign of organic disease of the vestibular or central nervous system.

Courtesy of World-Wide Abstracts

Bernstein, L.: Arch Otolaryng 76/4:329

Continued

BEST WISHES
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HYPERCALCEMIA IN CARCINOMA OF THE BREAST

The authors state that of the essentially asymptomatic patients with metastatic carcinoma of the breast, 10% will develop episodes of acute hypercalcemia. The symptoms are of (a) gastrointestinal, (b) central nervous system, or (c) skeletal origin. They are insidious and nonspecific, often imitating increased intracranial pressure and, by inference, metastatic brain involvement. If untreated, severe mental and physical deterioration and sudden death occur. With proper recognition and treatment, the hypercalcemia is reversible and the patients often live months to years asymptomatically.

The pathologic physiology is related to the sudden mobilization of large amounts of calcium from the skeleton. Hypercalcemia as a complication of malignant disease is rare unless there is metastatic bone involvement.

The authors studied 145 patients with metastatic breast carcinoma. Thirty-three of these had 59 episodes of hypercalcemia. There were (a) 41 spontaneous episodes, (b) 11 episodes related to hormone therapy, (c) two patients with disturbance in water balance, and (d) one episode following oophorectomy. Seventeen patients died either during the hypercalcemic episode or from their disease. Hypercalcemia causes death by cerebral depression or cardiac arrest. Prompt suspicion, diagnosis, and treatment are the essential factors in preserving the patient's life.

The treatment of hypercalcemia is either to decrease the rate of calcium mobilization or increase the rate of urinary excretion. The authors list the specific steps for each. Hormones may be either detrimental or helpful, as is surgical oophorectomy, adrenalectomy, and hypophysectomy. Radiation therapy and chemotherapeutic agents seem effective in controlling hypercalcemia. Intravenous fluids may be necessary to maintain effective urine output. Low calcium diet and artificial renal dialysis are also adjunctive treatment.
A worthwhile, well-written article that should be read closely by all physicians who care for this type of patient.

Jerome T. Grismer, M.D.
Minneapolis, Minn.

Jessiman, A. G., Emerson, K., Shah, R. C., and Moore, F. D.: Hypercalcemia in Carcinoma of The Breast. Ann Surg 157:377, 1963

HEART BLOCK

This paper consists of the minutes of a round table discussion presented at the 28th Annual Meeting of the American College of Chest Physicians in Chicago, June, 1962. The discussion largely concerns the internal pacemakers. There are two most important indications for the use of an artificial pacemaker. Its use is indicated in patients with repeated episodes of Stokes-Adams attacks which cannot be completely and reliably corrected over a long period of time by the administration of drugs. Use of an artificial pacemaker is also indicated in patients with complete heart block who do not have Stokes-Adams disease or whose Stokes-Adams attacks are well controlled, but who have a reduction in cardiac output so that their exercise tolerance and activity are severely limited.

Courtesy of References and Reviews
Journal of the American Medical Association

Dimond, E., Bay, E., Chardack, W., Dack, S., and Zoll, P.:
Dis Chest 43:456, May 1963

Continued

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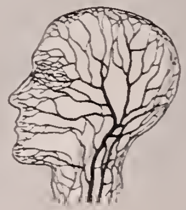

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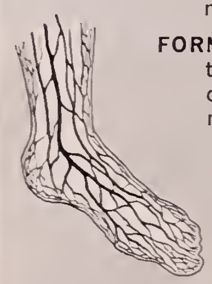

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MANAGEMENT OF JUXTARENAL AORTIC OCCLUSIONS

The incidence of patients with Leriche syndrome who have obstruction to flow at the level of the left renal artery varies from 3 to 15%. Although the management of distal aortic occlusive disease is fairly uniform, there has been no standardization of methods of reconstruction of the aorta at or above the renal artery level. The authors report their experience with a variety of technical aids including hypothermia, vasopressure agents, and osmotic diuretics in this complicated type of aortic occlusion.

In infrarenal aortic occlusion in which the thrombus reaches the level of the renal vessels the authors clamped the renal vessels and then the aorta proximal to the renal vessels. This prevented embolization. Endarterectomy of the thrombus was done with flushing of the residual thrombus from the stump of the aorta by releasing the clamps on respective vessels. The aortic clamp was then applied infrarenal. This is at normothermia or at hypothermia temperatures. Mannitol diuresis was possibly of some benefit postoperatively.

The authors then outlined their attack upon patients who had (1) aortic and left renal artery occlusion, (2) super-renal aortic thrombosis, and (3) aortic, renal, and mesenteric artery occlusion. They recommended that because of collateral involvement the entire upper aorta be exposed by developing the retropancreatic fusion fascia through a midline or paramedial incision. Systemic hypothermia at 30 or 31° C. was recommended as an adjunctive aid.

Because of the rapidity of placement, the authors preferred an infrarenal bifurcation prosthetic graft rather than thromboendarterectomy throughout the entire length of the occluded aorta in the reconstruction of the arterial bed.

Postoperatively every effort was made to return the patient to a normal physiologic state. Careful attention was paid to intravenous fluids. Angiotensin was the preferred vasopresser agent.

An article worth reading by surgeons who engage in vascular reconstructive work.

Jerome T. Grismer, M.D.
Minneapolis, Minn.

Bergan, J. J., and Trippel, O. H.: Management of Juxtarenal Aortic Occlusions. AMA Arch Surg 87:230, Aug. 1963

GASTRIC MUCOSA

A histological study of gastric mucosa by Wood's tube biopsy, made in 19 patients with active duodenal ulcer, was repeated after six weeks of ulcer regimen. Thirty-eight successful biopsies resulted in 91 specimens which revealed normal tissue in 63 (69%), superficial atrophic gastritis in two (3.3%), and atrophic gastritis in one (1.5%). The proportion of abnormal specimens (26.4%) during the acute phase did not change significantly after therapy (36.9%). Sampling error of multiple specimens obtained at any one biopsy was small (3.5%). In conclusion, the histological appearance of the gastric mucosa in acute and in healing phases was similar, and remission of symptoms appeared to be unrelated to the subsequent development of gastritis.

Courtesy of References and Reviews
Journal of the American Medical Association

DeLuca, V., and Spiro, H.: Arch Intern Med 111:363, March 1963

Continued

METHODS OF MEASURING RED-CELL LIFE SPAN

The availability and ease of red-cell labelling with Cr^{51} has made this isotope method the most widely used in measuring red-cell life span. DFP^{32} (di-isopropylfluorophosphate) has been used as an alternative method. This study compares the DFP^{32} and Cr^{51} techniques using C^{14} tagged glycine as the standard of reference. A variety of patients with malignant disease (multiple myeloma, leukemia, Hodgkins, etc.) were studied. Red-cell life spans obtained with DFP^{32} agreed well with those obtained with C^{14} tagged glycine. The data, however, showed that the Cr^{51} technique did not compare favorably with the C^{14} glycine and failed to reflect moderate shortening of red-cell survival in a significant number of cases. This was believed due to limitations of the method of Cr^{51} data analysis and because of the fact that there is a continual elution of Cr^{51} from intact red cells which occurs over a wide range in various diseases.

The authors concluded that because of simplicity and reliability, DFP^{32} techniques are the method of choice for red-cell survival studies.

Robert A. Green, M.D.
St. Louis Park Medical Center

Cline, M. J., Berlin, N. I.: An Evaluation of DFP^{32} and Cr^{51} as Methods of Measuring Red Cell Life Span in Man. Blood 22:459, October 1963

SURGERY OF ACUTE PERICARDITIS

At times emergency pericardectomy is necessary to relieve cardiac tamponade or constriction in patients with acute pericarditis. This need may arise despite the best of medical management and conservative pericardiocentesis. The etiology of the pericarditis is quite variable and is not the determinant as to the need for surgical interference.

Two types of surgical procedures have been performed, (A) localized drainage and (B) total pericardectomy.

The authors cite their experience with six patients and total pericardectomy for symptomatic pericarditis refractive to medical treatment. Their results are excellent.

Experimental evidence demonstrates that the inflamed pericardium is resistive to absorption of an effusion or the transmission of therapeutic antibiotic agents. The extreme rapidity by which effusion can cause tamponade as the intrapericardial pressure reaches 20 cm. + water explains the sudden cardiac collapse and death that may occur.

Although seemingly a radical procedure, early pericardectomy is conservative. The early procedure is relatively easy, the myocardial fibrosis and secondary organ changes are prevented, and the patient is spared months of invalidism.

Jerome T. Grismer, M.D.
Minneapolis, Minn.

Iturrino, J. L., Holland, R. H.: The Emergency Surgical Management of Acute Pericarditis. J Thoracic Surg 45:324, 1963

PATHOGENESIS OF THE ESOPHAGEAL VARIX RUPTURE

Twenty unselected patients with bleeding esophageal varices were included in this study. All patients bled massively a few hours prior to operation, and the time elapse between onset of bleeding and operation ranged from five to 56 hours. Eighteen of the 20 patients were operated upon within 16½ hours of the time when they first became aware of bleeding. A Levin tube was inserted in all patients and used to lavage the stomach with cold saline and to instil cathartics and antibiotics, but none of the patients received esophageal balloon tamponade. Biopsies of the distal esophagus were obtained from 15 of the 20 patients at the time of transesophageal ligation of the varices. In only one of the 20 patients was there gross esophagitis, and this was confirmed by microscopic evidence of inflammation. However, the remaining 14 specimens showed many dilated mucosal veins but no evidence of inflammation.

The authors then discussed the evidence in support of the acid peptic hypothesis of esophageal ulceration and secondary rupture of varicosities. They note that the laboratory work was done in animals, and that the pathological specimens on patients were usually done at the time of autopsy, or after the patients had had tamponade by an esophageal balloon. They felt that the major shortcoming of the autopsy and endoscopic studies showing the esophagitis associated with bleeding varices was that none of the studies were performed at the time of onset of the varix hemorrhage. They then cite other authors who found evidence against the role of gastric acid in the pathogenesis of the varix rupture. The authors do not feel that their particular study proved that increased portal hydrostatic pressure was responsible for the rupture of esophageal varices. Nevertheless, they felt that the hydrostatic pressure hypothesis remained the most logical and attractive explanation of the cause of bleeding from varices. They cite the lack of esophagitis at the time of transesophageal exploration and ligation of the varices in 19 of the 20 patients. The site of rupture was a small circumscribed laceration near the region of the esophageal gastric junction. The bleeding point had the appearance of a clean tear or hole on the mucosa overlying the varix from which blood spurted under considerable pressure. The mucosal defects were approximately 1 to 3 mm. in diameter, and had none of the characteristics of chronic ulcer or erosions.

An extremely interesting and timely article that deserves more consideration by both internists and surgeons.

Jerome T. Grismer, M.D.
Minneapolis, Minn.

Orloff, M. J., and Thomas, H. S.: Pathogenesis of the Esophageal Varix Rupture. AMA Arch Surg 87:301, Aug. 1963

No Accident

I never did anything worth doing by accident, nor did any of my inventions come by accident; they came by work.—Edison

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Progress

Unquestionably, there is progress. The average American now pays out twice as much in taxes as he formerly got in wages.—Henry Mencken

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—George Lorimer

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Book Reviews

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CAMPBELL'S OPERATIVE ORTHOPAEDICS-FOURTH EDITION — **A. H. Crenshaw, C. V. Mosby Co. 11/26/63. $57.50.**

The fourth edition of this thorough and carefully planned two-volume text maintains the high standard set by the previous editions. Each volume is handsomely bound and the print is excellent.

Most of the chapters have been entirely rewritten and carefully edited, and one third of the illustrations are new. The various isolated material on the hand presented in previous editions has been reorganized and expanded into a special 176-page section. New drawings picturing anatomical relationships and surgical approaches are particularly helpful in clarifying the operative techniques proposed.

The material is detailed enough to appeal to the orthopaedic specialist planning his next procedure and comprehensive enough to be of value to the generalist who needs an up-to-date reference in his office.

Harrison H. Farley, M.D.
Minneapolis, Minnesota

TRAUMA — **Medical Legal, Matthew Bender & Co., Inc. Albany, New York**

This small volume deals with the anatomy and physiology of the skin, dermatitis, and trauma to the kidneys. It should serve well as a reference for attorneys in medical legal court work. The book itself could be used to illustrate these phases of anatomy as they are being explained for a jury.

Carl O. Rice, M.D.
Minneapolis, Minn.

DISEASES OF THE HEART AND BLOOD VESSELS. **Nomenclature and Criteria for Diagnosis. By the Criteria Committee of the New York Heart Association. Sixth Edition. Little, Brown and Co. Boston. 1964. 463 pp. $5.50.**

The first edition of this reference was published by the New York Heart Association in 1928. In the intervening years it has become the referee in cardiology, defining terms, setting limits, and in general defining criteria for the labels in heart disease. In the five previous editions Harold Pardee was the principal author. Charles E. Kossman is Chairman of the Criteria Committee responsible for the sixth edition.

This is a unique work in medical literature, standing somewhere between a dictionary of cardiological terms and a diagnostic text book of heart disease. Many of the criteria and definitions are universally accepted. And the terms that may be unacceptable will serve as straw men for other authors to knock down.

Spatial vectorcardiography is mentioned, and the skeleton of an outline for description of spatial abnormalities is included. This reviewer ventures the guess that the seventh edition will have much more to say about this method of study of heart disease.

Reuben Berman, M.D.
Minneapolis, Minn.

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Special Articles

Present Status of Tuberculosis*

J. ARTHUR MYERS, M.D.
Minneapolis, Minn.

In the control of tuberculosis there is a sharp contrast between where we were when the present century opened and where we are today. Prior to 1900 the tuberculosis situation was so desperate that to many there was no hope of solution. However, there were a few courageous persons such as Sir Robert W. Philip of Edinburgh, Herman Biggs and E. L. Trudeau of New York State, Sir William Osler of Baltimore, Lawrence Flick of Philadelphia, and Longstreet Taylor of St. Paul, who had visions of the human race ultimately freeing itself from this disease.

Methods of Attack

In 1857 the Channing Home was opened in Boston for consumptives. A private sanatorium was established in Ashville, North Carolina in 1875, the Adirondack Cottage Sanitarium (later the Trudeau Sanatorium) at Saranac Lake in 1885, the first municipal hospital for poor consumptives at Cincinnati in 1893, and the first state sanatorium at Rutland, Massachusetts in 1898.

In 1892 and 1893 in Philadelphia and at Madison, Wisconsin, it was demonstrated that apparently healthy cattle harboring tubercle bacilli can be identified by the tuberculin test. Thus, for the first time the veterinary profession visualized ultimate eradication of tuberculosis among the animals of this country.

As this century opened these few sparks were fanned into flames. Of great importance was the dissemination of information among the citizenry everywhere concerning well established facts, particularly that tuberculosis is communicable. Therefore, in 1904, "The National Association for the Study and Prevention of Tuberculosis" (later the National Tuberculosis Association) was organized. In due time this Association had component organizations in each of the states and in many counties. Indeed, more than 2,500 such organizations, working in close co-operation with the National Association, were disseminating information concerning tuberculosis among our citizens everywhere. This led to rapid sanatorium building and increased support for the veterinarians to campaign to eradicate tuberculosis from animals. Continued education of the public resulted in numerous cases of communicable tuberculosis being taken from homes and communities and isolated in sanatoriums. Pasteurization of milk in cities, the flash-heat method in rural areas, and the nation-wide

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*Presented before the Mississippi Valley Conference on Tuberculosis, Minneapolis, October 11, 1963.

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tuberculosis-eradication-from-animals program markedly reduced the number of invasions of human bodies by the bovine type of tubercle bacilli.

Tangible Results

Among people of all ages the tuberculosis mortality rate in 1900 was 194.4 per 100,000. Thereafter, there was almost a continuous decrease down to 33.5 in 1947 and 5.2 in 1962, with a corresponding decrease in morbidity rates.

Present Status

Through prolonged, strenuous, and costly antituberculosis work tuberculosis was brought to its lowest ebb by 1961. Despite this accomplishment the road to eradication has been traveled less than half the way. Among the remaining gross problems are infections in people of the upper age brackets.

Why More Elderly People Have Tuberculosis

There are many persons living today who were born between 1890 and 1920. They, like the many generations before them, were subjected to invasions with mammalian tubercle bacilli (both bovine and human) when tuberculosis was at its height. Thus, among the children and young adults of that period so many became invaded by tubercle bacilli that the disease was destined to take its course throughout the remainder of their span of life. It was with these individuals that our sanatoriums were filled to capacity, with long waiting lists, and it was among these individuals that mortality rates continued at such high levels. Even now it is among these senior citizens that tuberculosis continues to take its greatest toll. In fact, in Minnesota in 1962 approximately 60 per cent of the deaths occurred in persons of 65 years or older. The morbidity and mortality from tuberculosis in the other states of the Mississippi Valley Conference area showed the same trend as in Minnesota, as we have all had approximately the same tuberculosis control program.

General Tuberculosis Control Program Has Been Inadequate

Although extremely effective, our control program has not been adequate, as evidenced by the fact that we have allowed the elderly to disseminate tubercle bacilli among a sizable segment of individuals of the younger generations.

The way we have dealt with tuberculosis may be likened to a modern fire department called day after day to extinguish fires set by arsonists. Tubercle bacilli may be likened to involuntary arsonists. We have allowed enough of the older persons with communicable disease to disseminate tubercle bacilli among persons of the younger generations to create a problem of considerable magnitude and one that will continue among these individuals as long as they live. Therefore, our tuberculosis problem today is not limited to persons in the upper age brackets but also to the younger generations whom we have allowed to become invaded by tubercle bacilli.

The following case illustrates the importance of accuracy of diagnosis. A man aged 58 had myelogenous leukemia diagnosed in his physician's office. Because of some symptoms referable to his chest he was admitted to a hospital on August 17, 1962. Roentgenographic inspection of his chest revealed an extensive area of disease in the upper lobe of the right lung, reported as possibly due to pneumonia but compatible with rather extensive leukemic infiltration. He was then discharged from the hospital. However, on October 2, 1962, he was readmitted for radiation of the pulmonary lesion. A new roentgenogram was reported as showing the previous finding in the upper lobe of the right lung with possible cavitation and an additional infiltrate in the superior segment of the lower lobe. It was then recommended that bacteriological studies be made. An abundance of acid-fast bacilli were found in the sputum. He was then admitted to a sanatorium where, on the usual routine, including antituberculosis drugs there was remarkable clearing of the shadow-casting lesions.

During the first stay of this man in the

Continued

hospital from August 17 to 22, 1962, and the second, from October 2 to 7, the hospital personnel employed no communicable disease technique. One of the nurses who cared for him from October 2 to 7 had had numerous periodic tuberculin tests as a student and also in hospitals where she subsequently worked. At no time had a reaction occurred. Toward the end of December 1962 this nurse of 29 years developed mild symptoms, including fatigue. She later had chills and fever, whereupon her physician prescribed penicillin, which was not helpful. In March she was given a course of acromicin without improvement. On April 20, 1963, she was admitted for more complete examination and diagnosis to the hospital where she had cared for the tuberculous patient. X-ray film inspection of her chest disclosed areas of infiltration in the upper lobe of each lung and in the midportion of the right lung. On April 22 the laboratory reported having found acid-fast bacilli in her sputum both on direct and concentrated smears. No source of exposure was found except the patient whose supposed leukemic infiltration was a tuberculous process. This nurse is now being compensated for having contracted tuberculosis in line of duty.

Practical Information Acquired

Although the announcement of the discovery of the tubercle bacillus was made in 1882, tuberculin produced in 1890, and X ray discovered in 1895, the full usefulness of these and other parts of our armamentarium awaited study and experience during the present century. For example, longitudinal observations were made on 2,000 girls and boys whose invasions with tubercle bacilli were acquired during infancy and childhood and who have been followed for several decades. These observations have established facts replacing many previous theories and opinions and have enabled us to chart a medically and economically sound tuberculosis eradication program.

Areas of tuberculous diseases begin to develop within an hour after tubercle bacilli invade. These lesions are prevented from causing much destruction of tissue and significant illness by the natural defense mechanism of the body. However, in a minority these lesions may later liberate tubercle bacilli on tissues that have become sensitized to the protein of the tubercle bacillus where they set up both acute and chronic forms of progressive tuberculosis, known as endogenous reinfection. Although this is a minority group, its present magnitude is indicated by the fact that tuberculosis causes more incapacity and death in the world than all other communicable diseases combined.

Tuberculin Reactors A Threat

The initial disease, resulting from the first invasion with tubercle bacilli, is known as primary tuberculosis. Early in this century this was thought to be the type of disease that caused the destruction manifested by meningitis, miliary dissemination, tuberculous pneumonia, etc. However, longitudinal observations revealed that these forms of tuberculosis are due to endogenous reinfection and that the primary disease per se is an exceedingly benign condition. Nevertheless, it results in sensitivity of tissues to the protein of tubercle bacilli and may later provide the tubercle bacilli that cause the more destructive forms of the disease. While this type of tuberculosis develops in a minority of reactors at some subsequent time, there is no way to identify those in whom it will appear. Therefore, all tuberculin reactors regardless of age are regarded as potential cases of clinical tuberculosis.

When invasions with tubercle bacilli can first be identified by the tuberculin test only five per cent or less of individuals so invaded present abnormalities on roentgenograms. The great majority of such persons go through life with no roentgenographic evidence of the disease. Therefore, X-ray film inspection of the chest alone misses 95 per cent or more of the persons whom the tuberculin test identifies as harborers of tubercle bacilli.

Roentgenograms Play Most Important Role at Age 12 and Thereafter

Roentgenographic inspection of the chests of tuberculin reactor children under the age of 12 years are of little value. Although chronic communicable tuberculosis occurs among the younger children, it has been reported only rarely. However, long-term observations among tuberculin reactor children have revealed that chronic pulmonary tuberculosis appears with sufficient frequency among children of 12 years to warrant that roentgenographic inspection be made beginning at age 12 and continuing throughout life. When made periodically roentgenograms detect evolving clinical tuberculosis on an average of two or three years before the hosts have external manifestations, before the disease is contagious, and while it is easily and satisfactorily treated.

Eradication Means Extermination of Tubercle Bacilli

Only the tuberculin test provides a sound starting point for the tuberculosis eradication program, eradication here referring to complete extermination of the bacilli and not just the prevention of morbidity and mortality. When there is no death from tuberculosis and no person requiring treatment for this disease there will still be a serious problem to maintain that status by giving adequate attention to the large number who will still be harboring tubercle bacilli.

With our present knowledge of the disease and with nothing more than our existing armamentarium there is no doubt that tuberculosis can be eradicated wherever and whenever people have the will to eliminate the disease forever.

For a long time methods of eradication have been recognized and strongly recommended. In fact the address of the President of this organization in 1947 was titled "Tuberculosis Eradication — Not Control." The following quotation is from that address: "The final clean-up will be the most difficult task in the entire conquest of tuberculosis. For the most part, we have done the easy, gross and crude work which may be likened to cleaning a floor with a coarse broom and a mop. For the final process we must get down on our knees and scrub with our hands; then polish and wax. In the final tuberculosis roundup, we must roll up our sleeves and test every person with tuberculin and thus find the tuberculosis the X ray has missed. Our efforts must then be concentrated upon the reactors to see that they are kept under close surveillance. Otherwise, some of those who are now healthy will become contagious and thus prolong the day when total eradication can be proclaimed.

It is my hope that this conference as an organization will continue to constitute the best group of tuberculosis workers in the world, with steadfastness of purpose, keeping faith with the public and unflinchingly destroying the tubercle bacillus until this enemy is driven from the Valley. By so doing, the entire world can continue to follow our example until tuberculosis is extinct everywhere."

Eradication Program Must Start with the Prenatal Period

If eradication is to be attained our program must start with the prenatal period. During this period every adult who is to have contact (including parents, grandparents, other relatives, domestics, nurses, physicians, etc.) must be examined and those found to have communicable tuberculosis dealt with accordingly. Children are born free from tubercle bacilli. Therefore, our most pressing problem is to see that they remain so. Wherever serious effort has been made to create for children an environment free from liberated tubercle bacilli, only an exceedingly small number of preschool children are now being invaded by tubercle bacilli. For example, in Boston in 1962 only 0.6 per cent (78) of the 14,064 1st grade children reacted to tuberculin. Thus, in 99.4 per cent the necessary precautions had been taken. However, eradication implies that no child react to tuberculin.

Certification of Schools Solves Many Problems

As children reach school age the number of their adult associates increases. Therefore, effort is required to insure protection against invasions from adult associates both inside and outside of school. The Committee on Tuberculosis of the American School Health

Continued

Association (Doctor A. O. DeWeese, Executive Secretary, Kent, Ohio) has promoted just such a program for more than two decades. After careful study and consideration the Committee concluded that the best method of solving the problem of tuberculosis in schools would be to officially certify schools on the basis of tuberculosis control work in progress. This has been done in close co-operation with state tuberculosis and health associations. Certificates are awarded those schools in which at least 95 per cent of the children in all the grades, including high school, are tested with tuberculin along with 100 per cent of the personnel. All high school and personnel reactors are examined promptly and periodically as long as they are in the school system. Those found to have clinical lesions are removed from schools but permitted to return to their regular work when their disease has been adequately treated. The certificates are signed by the president and executive secretary and the chairman of the state subcommittee of the American School Health Association and the executive director of the state tuberculosis and health association and in some cases, the state health officer. The certificates are renewed every two years after the entire original procedure has been repeated.

In most places where the Certification of Schools project has been employed the only difficulty has been experienced with personnel. Even in a large school one personnel member such as a bus driver, janitor or teacher refusing to have the test prevents the entire school from being certified. This situation has been overcome in some states by boards of health who have passed rulings, or legislators who have enacted laws requiring adequate pre-employment examinations and periodic examinations thereafter of all personnel members.

Practicing Poor Economy

We are now practicing extremely poor economy. It is stated that tuberculosis is costing this country approximately $750,000,000.00 annually. A large part of this expenditure is to provide hospital care, rehabilitation, etc., for persons whose disease was not found until it was so advanced that it required extended periods of treatment. Methods have been available for a long time by which nearly all chronic pulmonary tuberculosis can be diagnosed while it is still in the minimal stage and before it has become communicable.

The method recommended more than 30 years ago which consists of identifying all persons harboring tubercle bacilli by the tuberculin test and periodically examining the reactors would have markedly reduced the number of persons first found to have advanced disease and thus would have saved large sums of money and prevented numerous people from becoming invaded by tubercle bacilli. Although this costly time lag has been operating for more than 30 years it is not too late to start the program that is medically and economically sound. This will require an enormous expenditure in addition to the $750,000,000.00 now being spent annually; but when this procedure becomes effective the number of hospital cases will rapidly decrease with sharp reduction of cost, so that ultimately practically the only cost of the entire program will be for finding tuberculin reactors, periodically examining them, and providing for the relatively few who annually develop minimal lesions.

Present Work of Tuberculosis Associations Woefully Inadequate

It must be stated regretfully, that the present tuberculosis program in the Mississippi Valley Conferences area is progressing with only snail-like movement. Most of our organizations are doing this year about what they did last year and are planning for next year about what they are doing this year. Although slogans have been formulated and adopted with reference to tuberculosis eradication in some places, little has been done. With the present program tuberculosis cannot possibly be eradicated.

Please do not interpret these statements as criticism; they are merely factual. It is my opinion that under the circumstances we are doing all that is humanly possible. However, what we are doing is fragmentary compared with what must be done if eradication is to be accomplished. Because of lack of funds I do not believe there is an organization in the area that will be able to advance much beyond its present status. While the money derived from the sale of Christmas Seals and the occasional gift have been exceedingly helpful in the work of our organizations it does not represent a modicum of what is needed. Consider for a moment that tuberculosis is now said to be costing the United States $750,000,000.00 and that the total Christmas Seals sale for the entire nation yields only approximately $25,000,000,-00. While every effort should be made to continue the Christmas Seal sale and to increase our income from this source, we must now seek larger sums elsewhere.

An executive secretary of a municipal tuberculosis association refused to support an intensive clinical case-finding program recommended by the physicians in the area because funds from Christmas Seals were exhausted by what she was already doing and therefore it would be futile to take on more than her present funds would permit.

Adequate Funds Most Urgent Need

As the urgent need of our tuberculosis organizations is more adequate funds, the problem should be presented to state and federal legislators. If it is pointed out to them that eradication is the goal and that the recommended procedure is the most economical one there is little doubt that they will respond in the same generous way that their predecessors did in the tuberculosis control program.

Medical Organizations Willing To Donate Help

Medical organizations in this conference area have demonstrated willingness to contribute their professional services to the tuberculosis eradication program. For example, physicians outlined a McCloud County tuberculin testing program with adequate follow-up of the reactors. While they desired to donate their work, funds were needed for clerical workers, supplies, etc. A request was made from the county commissioners with the response that all necessary funds would be provided. In Meeker County in 1941 the medical society volunteered to administer the tuberculin tests, read roentgenograms and carry out all the medical procedures gratis for the entire citizenry of the county. To defray the cost of salaries of nurses, clerical workers, supplies, etc., the State Tuberculosis and Health Association, the National Tuberculosis Association, the State Medical Association, and the American Medical Association each donated one thousand dollars. One private citizen also made a donation. In the same state physicians have carried out similar projects in several other counties, municipalities and communities.

In the City and County of St. Louis, Missouri, annually since 1951, the members of the Academy of General Practice have conducted an intensive tuberculosis program in the schools on a gratis basis. Therefore, what is now being recommended is not based on theory or what might be done but on what has already been done in a few places and can be done everywhere.

Imperative That Local Physicians Participate

Above all we must never sell the medical profession short. It must be only physicians who are licensed to administer tuberculin tests, read roentgenograms, interpret laboratory reports, and make final diagnoses.

In Minnesota Doctor Herman Kleinmen, Chief, Section of Chronic Diseases, State Board of Health and former president of the State Tuberculosis and Health Association, is instituting a procedure which should prove extremely valuable. This consists of arranging for a short course at the University of Minnesota Continuation Study Center for physicians in December of this year. Among the subjects to be presented are administration, interpretation, etc. of the tuberculin test. A similar course has already been given for nurses.

Where surveys are conducted it is always best to have local physicians apprised of what is planned. Their participation in the surveys should qualify them for subsequent continuation of the various procedures which are so necessary in the eradication program.

Continued

To conduct a survey in a township, municipality or county independently of local physicians accomplishes little and may do permanent harm.

Lion's Share of Work Has Been Done by Nurses

Throughout the entire tuberculosis control program in the Mississippi Valley and, indeed, in the United States, nurses have done, are doing, and probably will continue to do the lion's share of tuberculosis work. Nurses have contirbuted magnanimously to every phase of the tuberculosis control program. Now they are playing a major part in the eradication program.

Co-operation of Health Officers Imperative

The tuberculosis eradication program is dependent in no small way upon local and state health officers and their co-workers, as only they have legal enforcement authority. Indeed, there is little to be accomplished by initiating an eradication program unless the health officials give it their enthusiastic support. In 1962 a Compendium of State Regulations and Recommendations Concerning Tuberculosis Screening of School Children revealed that very few of the health officers in our 50 states, the District of Columbia, and Puerto Rico now have any program for eradication. There are well nigh as many methods of dealing with the tuberculosis problem as there are health departments. Obviously, under such circumstances a nationwide eradication program could not succeed. This is one of the situations that our tuberculosis associations should promptly proceed to correct.

Emotional Displays and Controversies Should be Avoided

In the tuberculosis eradication program there is no place for emotional displays. The necessary procedures have been well documented, have been put to the test, and are on a sound basis. Numerous serious mistakes have been made by tuberculosis workers in the past by taking tangential excursions on unproved procedures. For example, Sanocrysin, a preparation made from gold was highly recommended without adequate documentation a few decades ago for the treatment of tuberculosis. Emotion ran so high that it was rather generally believed that no one was being adequately treated unless Sanocrysin was being administered. At this moment we are again in an emotional state concerning presently-used antituberculosis drugs. While there is no question about the value of these drugs in the treatment of both acute and chronic progressive forms of tuberculosis, it is well known that they are not germicidal; they do not destroy all tubercle bacilli in the human or animal body. However, they are so valuable in suppressing tubercle bacilli in areas of progressive disease that failure to use them in such cases might even be considered as malpractice.

At the same time it is known that they may create complications with serious consequences; in the presence of antituberculosis drugs some tubercle bacilli send out mutants which not only tolerate the drugs but thrive in their presence. These are spoken of as drug-resistant tubercle bacilli. Thus, new lesions which may develop from these resistant bacilli in the individual's body or in the bodies of persons whom he may infect may not be benefited by the drugs. Emotion is still running so high that antituberculosis drugs are now being used extensively for persons who have recently developed primary tuberculosis as manifested by tuberculin conversion and for children up to the age of three years who are found to react to tuberculin. These uses of drugs have not been adequately documented to recommend them except on an experimental basis.

Early Progress Still Most Valid

A fact of great significance is that the lion's share of tuberculosis control work was done before the antituberculosis drugs and pulmonary resection era. Thus, the methods employed prior to 1947 were exceedingly successful. There should be no let-down in their use because they are just as important and necessary today as they were before the antituberculosis drug era. Drugs and resection are only adjuncts and rightfully apply only to those cases in which tuberculosis has entered the last lap of its long journey in the human body.

Summary

The total eradication of the tubercle bacilli program consisting of determining the tuberculosis status of the 190,000,000 citizens of this country is not an insurmountable task. It needs to be done community by community, limiting the work of those conducting the programs to small populations to ensure completeness. The veterinarians covered every highway and byway, stopping at each home and testing all cattle, whether there was one or many per farm. The same technique is required for the eradication of tubercle bacilli from mankind. States of the Mississippi Valley Conference are second only to Iceland in the tuberculosis control program. There, this is the logical area for the true eradication program to be initiated with procurement of adequate funds by one or more of our state tuberculosis and health associations. This will require courage and dedication as well as long and arduous work.

Editors' note: Dr. Myers' article as presented above does not represent the total manuscript as submitted to us; however, we publish it herein in part because of its great interest and value to the medical field.

Quiz Program From the Middle Ages*

1. Is the necessity of death innate?
2. Does the fetus resemble the mother more than the father?
3. Is air more necessary than food or drink?
4. Is water more healthy than wine?
5. Is living on bread and water only healthy?
6. Is it healthy to get drunk once a month?
7. Is woman an imperfect work of nature?
8. Does a libertine life lead to baldness?
9. Which is the most healthy, wine mixed with water, pure water or pure wine?
10. Should literary men marry?

These were Doctoral Theses from the Middle Ages required of candidates for docteur regent or professor by the University of Paris. What is your score?

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*Reisman's Story of Medicine in the Middle Age

Debt

A new Beatitude might well read, Blessed are the young, for they shall inherit the national debt.—Herbert Hoover

---

Brothers

The answer to the question, "Am I my brother's keeper?" must always be "NO-! I am my brother's brother."—Paul Klapper

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Deeds Count

The smallest good deed is better than the grandest good intention.—Duguet

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Our facts must be correct. Our theories need not be if they help us discover important new facts.—Hans Selye

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President's Letter

I accompanied all four of the Governor's bus tours to state mental institutions as a representative of the Minnesota State Medical Association. These were held once a month from January through April. It must be noted that the tours covered so much territory that only sketchy observation was possible in any particular place. There was, however, an opportunity for the tour members to get a general idea of the present status of the care of citizens suffering from mental disease.

There is no question about the improvement in the care of mental patients. I think that Governor Youngdahl should have great credit for providing the initial impetus in this regard in the late '40's. Since then Governors Freeman and Rolvaag are notable for their effort in the same regard. Of course the timing was fortunate because their beliefs and goals were made much easier of execution by the development of the tranquilizing drugs. Without such drugs progress would have been much slower. For example, the "open-door" policy which is now adopted in general and the discontinuance of patient restraints which is widely followed would probably still not be possible. I look forward to an increasing use of drugs because I expect to see substances discovered which when administered alone or in combinations will be useful in treating specific mental abnormalities.

The old "asylum" idea in the care of mentally ill patients, though it is doubtful that it can ever be completely dropped, has been replaced by a genuine interest on the part of the responsible people for the prevention, control and reduction of mental illness and mental retardation. Workers at all levels in the Minnesota Mental Health Program seem concerned not only with the efficient operation of the institutions but also with the recognition of the patients as individuals with human rights. This attitude goes a long way toward making it possible to reclaim many persons formerly relegated to a lifetime of custodial care and nothing else. Many of these people are now being returned to satisfactory lives in communities. Education of the general public has helped make this possible — not many years ago a mental hospital patient dischargee found it practically impossible to obtain any sort of acceptance upon his return to his home or any other community.

Staffing of mental care institutions is steadily improving. Several factors are responsible. Legislative appropriations have increased. Psychiatrists are finding that professional and financial rewards in institutions are comparable with those of private practice. Psychologists are being trained in large numbers and they are taking over some of the burden formerly falling on psychiatrists. Rehabilitation experts and sociologists are being utilized to a greater extent. Institutions themselves are doing excellent on-the-job training of likely candidates to improve over-all staffing problems. Many of the insti-

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Prediction of Serum Cholesterol Changes Caused by Dietary Fat in Man*

FRANCISCO GRANDE, M.D.**
JOSEPH T. ANDERSON, Ph.D.***
Minneapolis, Minn.

CURRENT INTEREST in the dietary control of serum cholesterol concentration demands a knowledge of the effects of the various foodstuffs on the serum lipid levels in man.

Obviously much has still to be learned before we can have a complete understanding of the effects of the different nutrients on serum lipid levels, but the progress made in the last 10 years indicates that it is possible, within limits, to predict the changes in serum cholesterol concentration caused by certain dietary changes.

It is the purpose of this paper to present some of the pertinent information and to discuss the quantitative relationships between dietary changes and changes in serum cholesterol in man.

Dietary Fat and Serum Cholesterol Concentration in Man

Our present knowledge about the effect of the diet on serum cholesterol concentration in man is derived from two kinds of studies: epidemiological work and dietary experiments in the laboratory.

Effects of Different Fats

Epidemiological studies have shown that populations subsisting on diets with a high content of saturated fat have higher serum cholesterol levels than comparable populations subsisting on low fat diets or on diets containing predominantly oils rich in polyunsaturated fatty acids.[22,23,28] Controlled dietary experiments have shown that changes in serum cholesterol concentration can be produced in man by changing the amount and kind of dietary fat.[1,7,9,30]

---

*Supported by grants of the U. S. Public Health Service (Research Grant H-4401), the American Heart Association, the Minnesota Heart Association, the John A. Hartford Foundation, New York, and the Mount Sinai Hospital Research Fund.

**Jay Phillips Research Laboratory, Mount Sinai Hospital and Laboratory of Physiological Hygiene, University of Minnesota.

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It is generally agreed that other factors being constant, an increase in the proportion of saturated fatty acid glycerides in the diet increases serum cholesterol concentration, while an increase in the proportion of polyunsaturated fatty acid glycerides causes a decrease of cholesterol. Monoene fatty acids are indifferent, that is to say that when isocalorically substituted for carbohydrate they do not produce significant changes of serum cholesterol concentration.[19,25]

Molecular Size

It must be noted that the effect of the saturated fatty acids depends on the molecular size. Saturated fatty acids with 10 or fewer carbon atoms have little or no influence on serum cholesterol concentration.[8,13,17,21] The effect of the polyunsaturated fatty acids on the other hand does not increase with the degree of unsaturation. The highly unsaturated fatty acids with up to five and six double bonds existing in fish oils have approximately the same effect on serum cholesterol as equal amounts of linoleic acid with only two double bonds.[2,18]

These effects refer only to the human species. Animal experiments have shown[15,20] that there are significant differences in the responses of the serum lipids to dietary fat between man and animals. Accordingly the results of animal experiments cannot be applied to the prediction of serum cholesterol changes in human subjects.

The Influence of Other Dietary Factors

While the effect of dietary fat on serum cholesterol concentration is now well established, it should be noted that other dietary factors also influence cholesterol concentration. Recent work has yielded valuable data concerning the effects of dietary cholesterol,[3,4,8,10,11,12] of carbohydrates in the diet,[6,27] and of the unsaponifiable material of some vegetable oils.[8,16] The effect of these factors, however, will not be considered in this paper.

The Fatty Acid Composition of the Diet and Serum Cholesterol

Like all the natural fats, the fats used in the human diet are mixtures of glycerides containing various proportions of different fatty acids, and we have indicated that the different kinds of fatty acids have different effects on serum cholesterol concentration. The prediction of the serum cholesterol changes to be expected when the dietary fat is changed requires a knowledge of their quantitative relationships. A first attempt in establishing this relationship and the derivation of an equation for the prediction of the serum cholesterol changes from the changes in fatty acid composition of the diet was published by Keys, Anderson and Grande in 1957.[24] A complete analysis of their results appeared in 1959.[26] Only a brief resume of this work will be given.

The data which served as the basis for developing the prediction equation were obtained in middle-aged males, free of metabolic abnormalities, who were fed standard diets in which fats of different composition were exchanged isocalorically for each other or for an isocaloric amount of carbohydrate. After three weeks of subsistence on the different diets the changes of serum cholesterol were studied. The data available include 60 sets of dietary comparisons in groups of 12 to 27 individuals.

Variations of Fatty Acids

The basic hypothesis in the analysis of the data was that the effect of a given fat on serum cholesterol concentration is the resultant of the effects of the various kinds of fatty acids, and that each of the main groups of fatty acids has a specific effect independent of the effects of the others. We considered three main types of fatty acids: saturated, monoene (or monounsaturated), and polyene (or polyunsaturated). By multiple correlation analysis the coefficients relating the changes in the amounts of each group of fatty acids (expressed as a percent of the total calorie intake) to the serum cholesterol changes observed were calculated. This analysis showed the coefficient for the saturated fatty acids to be positive, the coefficient for the polyunsaturated fatty acids to be negative, and that for the monounsaturated fatty acids to be, statistically, not significantly different from zero. This last result indicates that changes in the amounts of monoene fatty acids in the diet were not associated with serum cholesterol changes. Accordingly the term for the monoene fatty acids was omitted and the equation expressing the relationship between the serum cholesterol changes ($\triangle$ Chol.) and the changes in dietary saturated and polyunsaturated fatty acids was written:

$$\text{Chol.} = 2.68 \triangle S - 1.23 \triangle P \qquad (1$$

In this equation $\triangle$ Chol. represents the change of serum cholesterol concentration in mg. 100 ml. and $\triangle S$ and $\triangle P$ respectively the changes in saturated and polyunsaturated glycerides expressed as a percent of the total calorie intake. This means that, other factors being constant, in these experiments the serum cholesterol concentration increased by 2.68 mg/100 ml. when the intake of saturated fatty acids increased by one percent of the total calories and that it decreased by 1.23 mg/100 ml. when the dietary intake of polyunsaturated fatty acids increased by one percent of the total calories.

Consequently a decrease of serum cholesterol concentration can be obtained by reducing the amount of saturated fatty acids in the diet, or by increasing the amount of polyunsaturated fatty acids. However, it is apparent that the cholesterol-increasing effect of the saturated fatty acids is about twice the cholesterol-depressing effect of an equal amount of the polyunsaturated fatty acids. Lowering of serum cholesterol by addition of polyunsaturated fat to a diet rich in saturated fatty acids requires therefore large amounts of the former. On the other hand, reduction of the amount of saturated fatty acids and their replacement by polyunsaturated fatty acids causes a marked reduction of serum cholesterol, without increasing the total amount of dietary fat.

Since the coefficient of $\triangle S$ in equation (1 is approximately twice that of $\triangle P$, it follows

TABLE I*

Saturated, Monounsaturated and Polyunsaturated Components in 100 Grams (900 Cal.) of Food Fats

The column XSS gives the "excess saturated fat" of 100 grams of food fat calculated from the equation: $XSS = s - \frac{1}{2} p$. This may also be called % XSS in the food fat. % XSS is numerically equal to the increase in serum cholesterol level (mg/100 ml.) predicted for the introduction of 100 gr. of the food fat into a 2400 Cal. daily diet isocalorically replacing carbohydrate

	Fat (Glycerides)				
Food Fat	s Sat. (grams)	m Mono-unsat. (grams)	p Poly-unsat. (grams)	XSS (grams)	p/s —
ANIMAL FATS					
Beef fat (from meat)	49	48	3	+48	0.1
Butterfat	68	29	3	+67	0.1
Chicken fat	34	44	22	+23	0.6
Pork fat, lard	40	50	10	+35	0.2
VEGETABLE FATS					
Cocoa butter	59	39	2	+58	0.0
Corn oil	18	26	56	−10	3.1
Cottonseed oil	25	21	54	− 2	2.2
Linseed oil	10	22	68	−24	6.8
Olive oil	18	65	17	+10	0.9
Peanut oil	17	61	22	+ 6	1.3
Rapeseed oil	6	72	22	− 5	3.7
Safflower oil	11	13	76	−27	6.9
Soybean oil	17	29	54	−10	3.2
Sunflower oil	17	29	54	−10	3.2
Walnut oil	16	28	56	−12	3.5

*From Anderson, Grande and Keys, 1964[5] that $\triangle$ Chol. is a linear function of $2 \triangle S - \triangle P$.

Limitations of the Prediction Equation

The limitations of the prediction of serum cholesterol changes from changes in the intake of saturated and polyunsaturated fatty acids have been discussed in detail by Keys, Anderson and Grande.[26] The equation, as already noted, has been derived from data obtained in groups of middle-aged men who had average serum cholesterol levels between 200 and 250 mg/100 ml. when they were eating diets of the usual U. S. type of about 3000 calories per day with total fat providing 40 to 45 percent of the total calories, cholesterol intake of the order of 600 mg/day, and in caloric equilibrium (that is to say that their body weights were kept constant throughout the experiments). No satisfactory prediction is expected when the equation is applied to data obtained from men who differ from these specifications and under different conditions. However, equation (1 has predicted with reasonable accuracy the serum cholesterol changes reported by other workers when applied to their data.[1,21,31,32] More recently a satisfactory agreement has been found between the serum cholesterol changes predicted by this equation and the actual changes reported by Kinsell.[14,29]

This may be considered an indication of the validity of the prediction equation, and of its usefulness as a guide to the changes of serum cholesterol to be expected from a given change in the fatty acid composition of the diet.

The Prediction of Serum Cholesterol Changes in Individuals

While the prediction of average changes of serum cholesterol in groups of individuals is satisfactory in experimental work, the clinician will be more interested in the prediction of changes in single individuals. This obviously involves greater difficulty; but our experience indicates that it is possible to predict changes in individuals when their serum cholesterol concentration on a standard diet is known.

Hypercholesterolemic Gives Greater Response

It is generally accepted that men who are intrinsically hypercholesterolemic respond to a given dietary change with greater cholesterol changes than men who are intrinsically hypocholesterolemic. Keys, Anderson and Grande[26] have derived an equation for the prediction of the serum cholesterol change of an individual, as a percent of the average cholesterol response of the group, when his serum cholesterol concentration (as a percent of the average cholesterol concentration of the group) is known. The equation is:

$$\triangle \% = 1.91 X \% - 91 \qquad (2$$

in which $\triangle \%$ represents the individual serum cholesterol change as a percent of the average change of the group and $X\%$ the serum cholesterol of the individual as a percent of the average of the group on the standard diet. Assuming the average serum cholesterol of the experimental groups to be of the order of 225 mg/100 ml., when on a usual American diet, it is possible to calculate the percent change of cholesterol of a given individual using equation (2. Applying this value to the prediction obtained by equation (1 will give the change expected for this individual.

The Iodine Value and the Polyunsaturated: Saturated Fat Ratio

Because of the present interest in the dietary control of serum cholesterol concentration in man, there is also great interest in finding an expression which can be used as an index of the effect of a given fat on serum cholesterol concentration.

It will appear from the foregoing discussion that the effect of a given fat on serum cholesterol concentration depends not only on the actual composition of the fat in terms of the two main groups of fatty acids (saturated and polyunsaturated), but also on the total amounts of fatty acids in relation to the calorie intake. Consequently any index based on the chemical properties of the fat, but not including the proportion of calories, will be of only limited value.

Iodine Value

Iodine value has been suggested as a possible index of the effect of a given fat on serum cholesterol concentration,[1,29] but we have discussed the reasons why iodine value, alone or in combination with the amount of fat, is a poor predictor.[24,25,26] The iodine value of a fat is a measure of the number of double bonds. We can imagine two fats having a similar iodine value, one having only oleic acid while the other has only linoleic (half the amount). The first fat according to our experience will not produce any significant change of serum cholesterol when isocalorically substituted for carbohydrate, while the second fat having linoleic acid will produce a decrease of serum cholesterol. Moreover, we have already indicated that fish oils, rich in highly unsaturated fatty acids and with high iodine value, do not have a greater cholesterol-depressing effect than vegetable oils containing an equivalent amount of linoleic acid, and having much lower iodine values.[2,18]

Polyunsaturated:Saturated Fat Ratio

The same comments apply to the polyunsaturated:saturated fat ratio which is much used at the present as an index of the effect of a fat on serum cholesterol concentration. It is obvious that highly unsaturated fats (with a high polyunsaturated:saturated fat ratio) will tend to produce lower serum cholesterol than fats lower in polyunsaturated and rich in saturated fatty acids (low polyunsaturated:saturated fat ratio), but the quantitative effect will depend also on the amount of fat which is used.

The fact that the serum cholesterol change, according to our studies, is a linear function of twice saturated minus polyunsaturated (2S-P) does not mean that it is also a linear function of polyunsaturated: saturated fat. The first expression, as noted, depends on the amount of fatty acids expressed as a percent of the total calories, while polyunsaturated:saturated fat, being a ratio, is independent of the total amount of fat and of the units in which the fatty acid composition is expressed. A discussion of the relationship between twice saturated minus polyunsaturated (2S-P) and polyunsaturated:saturated fat has been published recently.[14] Here we should like to emphasize that the polyunsaturated:saturated fat ratio is only a qualitative indication of the effect of a given fat on serum cholesterol concentration.

The Prediction Equation

It has been noted that the effect of a given fat on serum cholesterol concentration depends on the difference between the amount of saturated glycerides and the amount of polyunsaturated glycerides that it contains.

Effect of a Given Fat on Serum Cholesterol

Since the cholesterol-raising effect of the saturated fatty acids requires twice the same amount of polyunsaturated fatty acids to be neutralized, the net effect of adding to the daily diet (s) grams of saturated fat and (p) grams of polyunsaturated fat is then equal to that of (s — ½p) grams of the saturated fat alone. As an example, the addition of a fat containing 20 grams saturated glycerides and 10 grams of polyunsaturated glycerides is equivalent to the addition of 20 — ½ (10) or 15 grams of saturated glycerides. The value (s — ½p), may be considered as the corrected value of saturated fat and may be called the "excess" of saturated fat, represented by the symbol XSS. We can write[5]

$$XSS = s - \tfrac{1}{2}p \qquad (3$$

XSS is positive when $s > \frac{1}{2}p$ and negative when $s < \frac{1}{2}p$. In the first case the fat will be expected to elevate serum cholesterol concentration; in the second case the fat will be expected to lower it. No change of serum cholesterol is expected if $s = \frac{1}{2}p$.

Effect of Total Calories on Serum Cholesterol

It has been shown experimentally[7,24] that the effect on serum cholesterol level of dietary saturated and polyunsaturated fats depends on their amounts in relation to the total caloric value of the diet. The terms S and P in equation (1 represent the amounts of dietary saturated and polyunsaturated glycerides expressed as a percent of the total calorie intake, while XSS in equation (3 represents grams of saturated glycerides. In order to determine the effect on serum cholesterol of such an amount of saturated glycerides it is necessary to express XSS as a percent of the daily calorie intake. Taking 9.0 calories per gram as the caloric value of the saturated glycerides, the caloric value of one gram of saturated fat as a percent of that of the total daily dietary intake will be:

$$\frac{9 \times 100}{\text{Cal.}} \qquad (4$$

where Cal. = total dietary intake in calories per day.

Equation (1 shows that one percent of calories from saturated fat will increase the serum cholesterol level by 2.68 mg/100 ml. Therefore, the cholesterol change (c) produced by one gram daily of saturated fat and expressed as mg/100 ml. of serum will be:

$$c = \frac{9 \times 100}{\text{Cal.}} \times 2.68 \qquad (5$$

But $9 \times 100 \times 2.68 = 2412$; consequently if the daily dietary intake is equal to 2400 Cal. per day the value of c in equation (5 becomes, 2412/2400, or practically one.

One Gram Saturated Fat Increases Serum Cholesterol by 1 mg/100 ml.

In other words, the addition of one gram of saturated fat to a diet providing 2400 Cal. day will be expected to raise serum cholesterol concentration by 1 mg/100 ml. Consequently the value XSS will represent directly, in mg. of cholesterol per 100 ml. of serum, the change of serum cholesterol level when (s) and (p) grams respectively of saturated and polyunsaturated glycerides are introduced into a daily diet of 2400 calories, replacing an isocaloric amount of carbohydrate. The change (c) of serum cholesterol level expected for the same dietary exchange in a daily diet of caloric value different from 2400 calories can be calculated by using the following equation:

$$c = \text{XSS}\left(\frac{2400}{\text{Cal.}}\right) \qquad (6$$

in which Cal. represents the total daily dietary intake.

This equation can be used to predict the effect of isocaloric substitutions of any two food fats. If fat number one is replaced by fat number two the expected change in serum cholesterol concentration ($\triangle$ Chol.) will be:

$$\triangle \text{ Chol.} = \text{XSS}_2\left(\frac{2400}{\text{Cal.}_2}\right) - \text{XSS}_1\left(\frac{2400}{\text{Cal.}_1}\right) \qquad (7$$

The serum cholesterol changes produced by exchanging two fats can then be estimated if we know the XSS values of the fats and the total calorie intake in the two dietary situations.

The XSS values of some common fats are given in Table 1 for 100 gram portions.

In the same table we have included for comparison the P/S values of the fats. The XSS values reported in Table 1, as has been noted, are numerically equal to the serum cholesterol change (in mg/100 ml.) predicted for the incorporation of 100 grams of the fat into a daily diet of 2400 Cal., isocalorically replacing carbohydrate. These values give therefore a direct measure of the effect of a given fat on serum cholesterol concentration, when fed under these specific conditions to groups of normocholesterolemic individuals.

Equation for Individual Change

The XSS values can also be used for the prediction of individual changes, following the reasoning presented in the section on prediction of individual changes. $\triangle$ % in equation (2 can be expressed

$$\triangle \% = \frac{c_i}{c_g} \times 100 \qquad (8$$

where c_i = individual cholesterol change and c_g = mean cholesterol change of the group, both in mg/100 ml. of serum.

X% in equation (2 can be expressed as

$$\text{X\%} = \frac{\text{Chol.}}{225} \times 100 \qquad (9$$

where Chol. indicates the serum cholesterol of the individual on the standard diet. Substituting the expressions for $\triangle$ % and X% given by equations (8 and (9 in equation (2, making $c_g = c$ in equation (6 and solving for c_i, we can write:

$$c_i = \left(1.91\,\frac{\text{Chol.}}{225} - 0.91\right)\left(\text{XSS}\,\frac{2400}{\text{Cal.}}\right) \qquad (10$$

Equation (10 makes possible the estimation of the cholesterol change expected in a given individual (c_i) if we know his serum cholesterol on the standard diet, the XSS value of the dietary substitution made and the caloric value of this diet. It can be seen that equation (10 is similar to equation (6 but that a correction factor has been introduced to account for the different intrinsic responsiveness of individuals. Similarly equation (7 may be applied to the prediction of the individual cholesterol change ($\triangle$ Chol.$_i$) when one dietary fat is substituted for another. The corrected equation (7 will be written

$$\triangle \text{ Chol.}_i = \left[1.91\,\frac{\text{Chol.}}{225} - 0.91\right]\left[\text{XSS}_2\,\frac{2400}{\text{Cal.}_2} - \text{XSS}_1\,\frac{2400}{\text{Cal.}_1}\right] \qquad (11$$

As an example, if we substitute 100 grams of corn oil for 100 grams of butterfat in the daily diet of a man who requires 3000 Cal. daily to maintain body weight and who on a usual diet has a serum cholesterol level of 337 mg/100 ml., the serum cholesterol change can be calculated as follows, from equation (11:

$\text{Chol.}/225 = 337/225 = 1.50$
$\text{XSS}_2 = -10$; for 100 grams corn oil
$2400/\text{Cal.}_2 = 2400/3000 = 0.80$
$\text{XSS}_1 = +67$; for 100 grams butterfat
$2400/\text{Cal.}_1 = 2400/3000 = 0.80$
$\triangle \text{ Chol.}_i = [1.91\ (1.50)\ -0.91]\ [-10\ (0.80) - 67\ (0.80)]$
$= (1.955)\ (-61.6)$
$= -120$ mg/100 ml., the negative sign indicating a *decrease* in level.

In this expression the first bracket on the right side is the correction for intrinsic cholesterol responsiveness which in this man is almost two because his intrinsic cholesterol level is high, 1.50 times "normal." The second bracket on the right is the cholesterol change expected in persons with a level of 225 mg/100 ml. on the usual diet, a decrease of 62 mg/100 ml. in this case. The application of these equations to the prediction of the cholesterol changes under different conditions is summarized in Table 2.

Summary

The analysis of a series of controlled dietary experiments in man has shown that the serum cholesterol changes produced by changing the fat in the diet are related to the change of saturated and polyunsaturated glycerides of the diet.

An equation was derived to predict the serum cholesterol changes in normocholesterolemic middle-aged men receiving a diet that maintains the body weight constant, when the dietary substitutions are made isocalorically.

Other factors being constant, an increase of saturated glycerides corresponding to one percent of the total calories of the daily diet causes a mean serum cholesterol increase of 2.68 mg/100 ml. A similar increase in the content of polyunsaturated glycerides of the daily diet causes a mean serum cholesterol decrease of 1.23 mg/100 ml.

The equation, with a correction factor, can be used to predict the serum cholesterol changes in other individuals when their serum cholesterol concentration on a standard diet is known.

The effect of a given fat on serum cholesterol concentration is expressed by its "excess of saturated fat" value (XSS). The XSS values of some dietary fats are given.

Equations have been derived to predict the serum cholesterol changes under various conditions using the XSS value of the fats. The application of these equations is described and examples of the calculations are given.

TABLE 2

Summary of formulas for the prediction of serum cholesterol changes from the XSS values of the food fats, under different conditions*

Condition		
Daily caloric intake	Substitution	Cholesterol change mg/100 ml.
A) For men with serum cholesterol 200-250 mg/100 ml. when on a usual American diet.		
$= 2400$	Fat for carbohydrate	XSS
$= 2400$	Fat 2 for Fat 1	$\text{XSS}_2 - \text{XSS}_1$
$\neq 2400$	Fat for carbohydrate	$(2400/\text{Cal}) \times \text{XSS}$
$\neq 2400$	Fat 2 for Fat 1	$\text{XSS}_2\,(2400/\text{Cal}_2) - \text{XSS}_1\,(2400/\text{Cal}_1)$
B) For men with serum cholesterol outside the range 200-250 mg/100 ml. when on a usual American diet		
$= 2400$	Fat for carbohydrate	$[1.91\,(\text{Chol}/225) - 0.91] \times \text{XSS}$
$= 2400$	Fat 2 for Fat 1	$[1.91\,(\text{Chol}/225) - 0.91] \times (\text{XSS}_2 - \text{XSS}_1)$
$\neq 2400$	Fat for carbohydrate	$[1.91\,(\text{Chol}/225) - 0.91] \times (\text{XSS}\,(2400/\text{Cal})$
$\neq 2400$	Fat 2 for Fat 1	$[1.91\,(\text{Chol}/225) - 0.91] \times [(\text{XSS}_2(2400/\text{Cal}_2) - \text{XSS}_1(2400/\text{Cal}_1)]$

*These formulas apply to men maintaining constant body weight. XSS corresponds to the amount of fat exchanged.

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16-32 will appear in reprints or can be obtained from the author.

St. Anthony's Fire

Erysipelas

St. Anthony's Fire, an antiquated but intriguing synonym for erysipelas and ergotism, was a disease of the Middle Ages: a rampant and baffling plague that left many of its victims either mutilated or dead. It afflicted Europe, especially France, in epidemic form from 993 until the 14th century. During the 11th century at the height of the pestilence the Order of St. Anthony founded hospitals to care for the victims; also numerous shrines appeared where the afflicted might sue for relief through St. Anthony's intercession.

Thus St. Anthony became the patron saint of victims of the disease, variously and appropriately known as ignis occultus or ignis sacer, de mal des ardents or maladie des ardents, holy fire or hell's fire, because of its flame-like spread on the skin and fiery sensation in the tissues.

Haggard dramatically describes the dreadful affliction thus: "In its common form the disease affected the extremities; an icy chill developed in the arms and legs and this was succeeded by a torturing burning sensation. As though consumed by internal fire, the limbs became black, and then shriveled and fell from the body. Some of those afflicted with the disease died, but many recovered, maimed and distorted even by the loss of all their limbs, so that there was left only the trunk and head."*

The Holy Order of Vienna reputedly had a collection of withered and blackened limbs which remained for some time at their hospital: mute and horrible evidence of the Fire's toll.

Though the cause of the disease was then unknown, the holy men of the Order of St. Anthony, who wore a blue T on their left shoulders, probably to represent a crutch, cared for the plague victims as well as they could in their hospitals, the doors of which were significantly painted red.

In 1597 the mystery of the source of the scourge was solved when, after investigation, the Marburg medical faculty concluded that it was produced by eating rye contaminated with the fungus growth, ergot.

Whence the name ergotism.

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*Haggard, Howard W.: Devils, Drugs, and Doctors p. 117.

Erosion of the Ureter with Urinary Extravasation due to Impacted Calculus

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EXTRAVASATION OF urine from the renal pelvis occurring secondary to calculi in the pelvis, although uncommon, has been reported in the past. However, after careful perusal of the literature, we have been unable to find any reported cases of calculus erosion of the ureter with extravasation. Following is a case report of perinephric and periureteral extravasation due to impacted ureteral calculus with erosion, but without prior instrumentation.

Case Report

A 57-year-old married registered nurse was admitted, acutely ill with abdominal pain, to the Mount Sinai Hospital, Minneapolis, Minnesota, on June 9th, 1963. The patient's past history included a cholecystectomy in 1944, an abdominal hysterectomy in 1949 for uterine myomata, and an episode of pyuria in January 1963, which cleared on tetracycline therapy.

On the current hospital admission the patient presented with a ten-hour history of acute and severe abdominal pain, nausea and vomiting. The pain was located in the epigastric area, was intermittent in nature, and radiated to the substernal region, left lower abdominal quadrant, and to the left flank and back. There were no associated urinary symptoms and no chills.

On physical examination the patient was a well developed, slender white female appearing dehydrated and acutely ill. Her temperature was 100.4 F. orally, blood pressure 120/80. Examination of the abdomen, in addition to the incisions from previous surgery, revealed generalized tenderness of the abdomen and rigidity on the left side. The left costovertebral angle area was exquisitely tender to palpation. The remainder of the physical examination, including pelvic examination, was essentially negative.

Urinalysis on admission showed one plus albumin, 10-15 rbc per high-power field and 5-10 wbc per high-power field. Catheterized urine culture subsequently grew out proteus. White blood count on admission was 12,000 with 89 neutrophils and 11 lymphocytes. Blood urea nitrogen was 16 mg. per cent. Chest X ray was negative and electrocardiogram was normal.

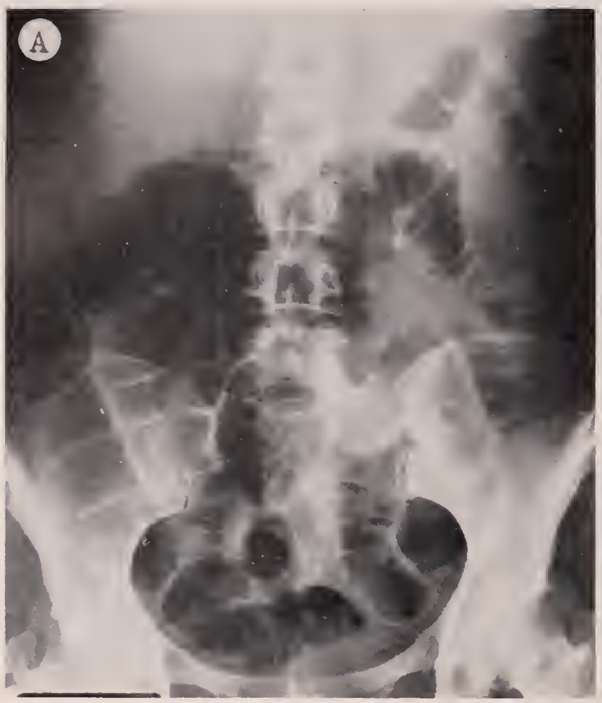

Fig. 1 — Preliminary KUB film of intravenous pyelogram series, 6/10/1963. Two calcifications present in the left upper quadrant. Note also marked degree of ileus.

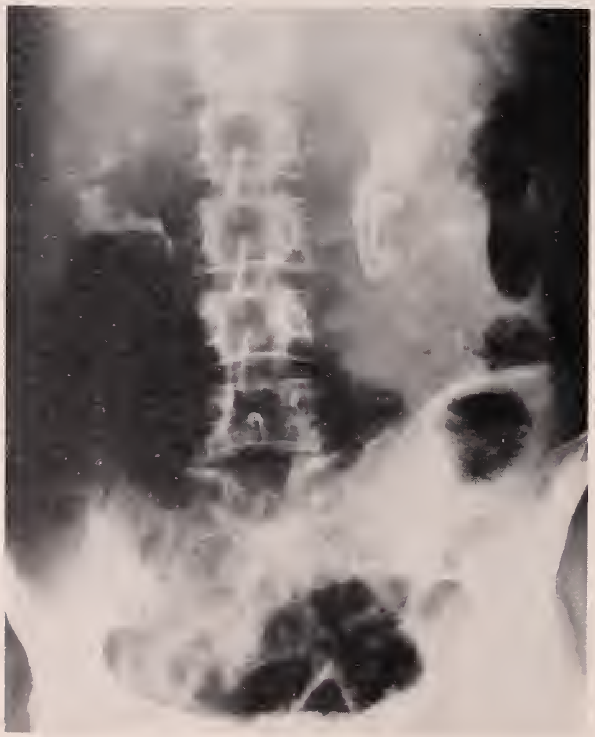

Fig. 2 — Intravenous pyelogram film 6/10/1963. Lower calcific density is seen to be calculus in upper lumbar ureter. Note extravasated contrast material in this area.

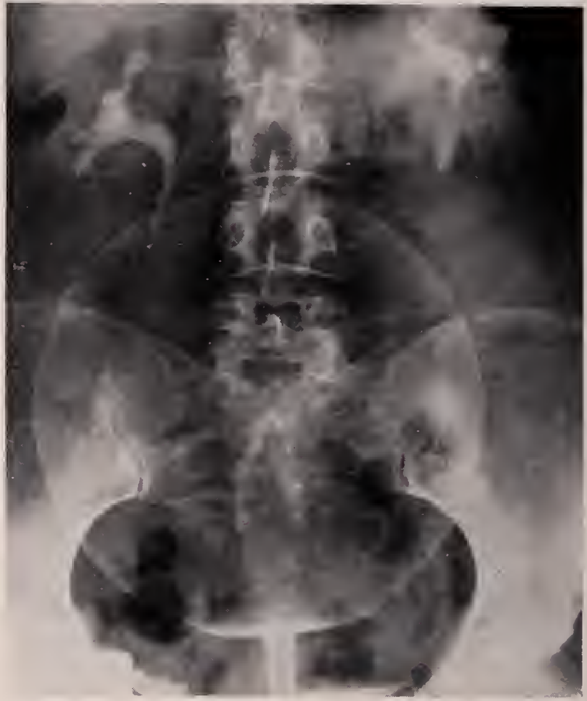

Fig. 3 — Intravenous pyelogram film taken eight weeks following surgery. Minimal dilatation of calyceal system is present, but drainage is adequate as evidenced by contrast material in pelvic ureter.

Flat plate of the abdomen taken on the day of admission showed two calcific densities in the left upper abdominal quadrant. Intravenous pyelography was carried out on the following day. On the preinjection film of this series (Fig. 1) one can see the two calcific densities, one lying lateral to the L_1 — L_2 interspace, the other lying lateral to the L_3 — L_4 interspace. After intravenous injection of contrast (Fig. 2), the most superior calcification is seen lying presumably in the middle calyceal system. The lower calcification can be seen lying in the upper lumbar ureter with extravasation of contrast material into the periureteral tissues.

Because of the findings of urinary extravasation and ureteral calculus on intravenous pyelogram, the patient was taken directly to surgery. Under general anesthesia the left flank was explored through a subcostal incision. A large amount of fluid was found in Gerota's fascia. The left ureter was markedly thickened, inflamed and friable, and the point of erosion in the wall could be seen with the calculus protruding. Ureterolithotomy was accomplished through a linear incision. No sutures were placed in the ureter, and no attempt was made to remove the renal calculus. Closure of the wound was effected in layers, two large penrose drains being used for drainage.

Postoperatively the patient's course was complicated by prolonged ileus, requiring several days of nasogastric suction and intravenous fluids. She also had a febrile course which relented on June 22nd following spontaneous drainage of a large amount of purulent fluid through the drain site. She was discharged on June 27th and has had no further difficulties.

A repeat intravenous pyelogram on August 2nd (Fig. 3) shows slight dilatation of the left calyceal system, but good emptying as evidenced by the visualization of contrast material in the left pelvic ureter.

Discussion and Conclusion

This case report is that of a patient who was without previous urinary symptoms, except for one episode of pyuria, and presented with the acute onset of severe abdominal complaints. Two calculi were found in the left renal collecting system, the one calculus having partially eroded through the lumbar ureter, producing urinary extravasation and accounting for the patient's symptoms. The unusual feature of this case is that the extravasation occurred without previous retrograde pyelography or other instrumentation.

At surgery the erosion in the ureter could be visualized and a considerable amount of purulent urine was found extravasated about the ureter and kidney. The obstructing calculus was removed and drainage of the retroperitoneal space established. The intrarenal calculus was not disturbed because of the degree of infection present and danger to the kidney if removal were attempted.

WHAT'S YOUR DIAGNOSIS?

A forty-seven-year-old white female had an elective cholecystectomy. Because of obesity, the procedure was more prolonged than usual and a deeper plane of anesthesia was required. She was drowsy in the postoperative period. Seven hours postoperatively she developed tachycardia and the temperature rose to 104°. When seen by the consultant she had shallow respirations with abdominal splinting. She was quite drowsy and unwilling to cough. The other pertinent physical examination demonstrated areas of E to A change, bronchial breathing, dullness at the right base, and poor diaphragmatic motion.

Pertinent laboratory work at that time demonstrated a leukocytosis of 16,350 with an increase in the polymorphonuclear white cells. Hemoglobin was 12.3 grams.

What is your diagnosis? Turn to page 678.

BLUMBERG'S SIGN

This is the rebound tenderness sign. In exerting pressure on the left iliac fossa and suddenly releasing the pressure of the hand, the patient experiences sudden pain in the lower abdomen.

Evolution

The karygranulomes, not the idiogranulomes or microsomenstratum in the protoplasm of the spermatogonia, unite into the idiosphacrosome, acrosoma of Lenhossek, a protean phase, as the idiosphacrosome differentiates into an idiocrytosome and an idiocalyptosome, both surrounded by the idiosphacrotheca, the archoplasmic vesicle; but the idioectosome disappears into the metamorphosis of the spermatid into a sphere, the idiophtharosome. — William Osler

Editor's Note: No wonder it's so hard to make progress.

Those who sit on the Left bank and howl at the Right neither facilitate the flow of the river nor adorn their own bank as the river flows by. — T. V. Smith

Giant Cell Arteritis of the

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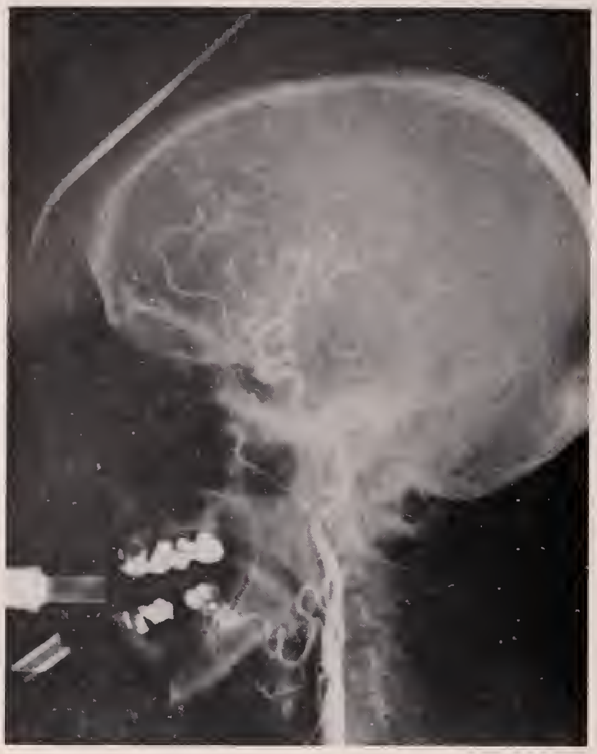

Fig. 1 — Right lateral internal carotid angiogram shows some anterior shift of the anterior cerebral division and some elevation of the middle cerebral. In spite of this the changes on this early arterial phase are nonspecific.

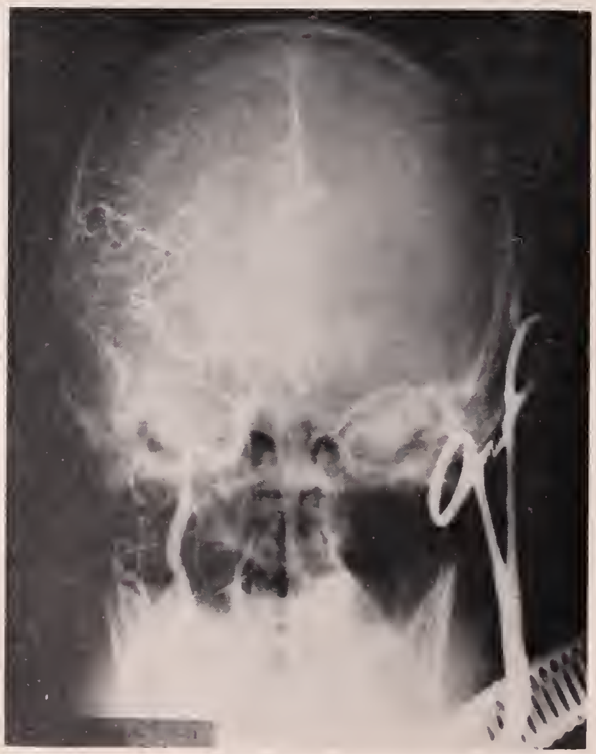

Fig. 2 — Anteroposterior view of the internal carotid angiogram on the early arterial phase shows displacement of the anterior cerebral vessels shifted to the left of the midline.

GIANT CELL arteritis of the brain and its coverings is extremely rare. As noted by Budzilovich,[3] only eight cases were reported in the literature prior to his inclusion of two additional cases. To my knowledge, no specific reports concerning the roentgen findings of giant cell arteritis are available. By way of contrast, temporal arteritis, a lesion which is histologically similar, is a common, benign lesion of the aged population. To emphasize this point, the literature was reviewed. Some eighty-four articles on the subject of temporal arteritis were published in the past three and one-half years alone, forty-one of which were within the last year itself. Obviously, there is no need to list these in the bibliography. Only a limited number are available concerning brain involvement.

Because of its rarity in contrast to the commonplace temporal arteritis, a report of a case with its roentgen manifestations is considered warranted.

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Central Nervous System

The Place
of
Roentgen Diagnosis

Case Report

The patient, a 67-year-old white female, was admitted to Mt. Sinai Hospital, Minneapolis, with a three-week history of nausea and vomiting.

Three months prior to admission she had developed right frontal headaches. Empirin compound was used for pain relief until the above-mentioned nausea and vomiting developed.

Positive findings were limited. There was some stiffness of the neck on flexion. The right carotid pulse was diminished. No bruit was present. The pupils and fundi were normal. There was left homonymous hemianopsia. Bilateral Oppenheim signs were elicited, and some impairment of the left heel to shin test was found.

Laboratory Findings:

Spinal fluid had nine white blood cells of which five were neutrophiles and four mononuclears. Protein was 232 mgm.%. Electrophoretic studies of the hemoglobin were normal as were all routine laboratory studies. The electroencephalogram showed markedly abnormal findings in the form of constant slow activity in the right hemisphere, suggesting a space-occupying lesion in the right frontotemporal area, probably toward the base.

Bilateral carotid angiogram was performed on 7-26-63 and showed abnormality on the right (Figs. 1-3). There was diffuse involvement of the right frontoparieto-temporo-occipital regions with shift of the anterior cerebral artery to the left of the midline. In spite of the massive distortion of the entire vascular bed by the space-occupying defect,

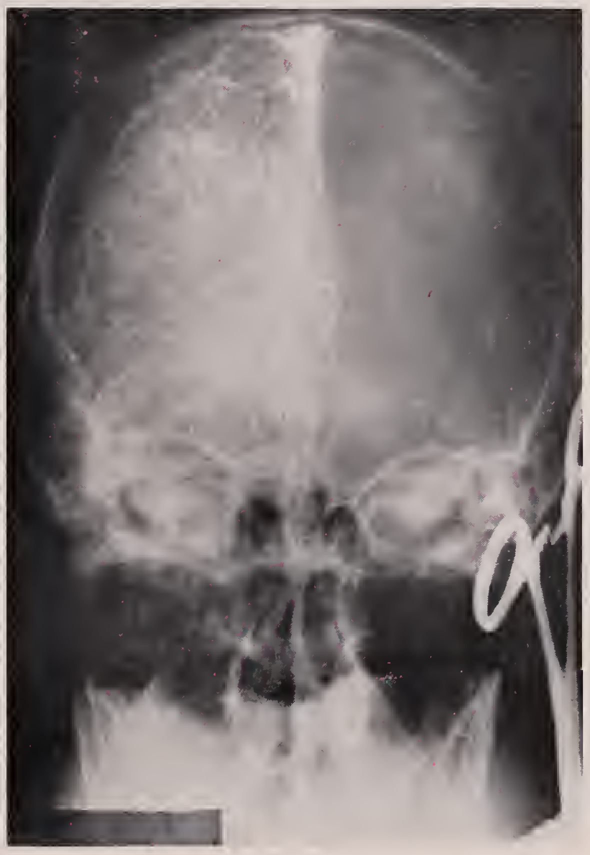

Fig. 3 — Intermediate (arterial-venous) phase of anteroposterior projection of internal carotid angiogram showing the finding which the author thinks is most significant, i.e., attenuation and straightening of the smaller vessels, different from generalized edema or tumor vessels.

classical vessel displacement of tumor, abscess, or cyst was not present. In spite of this, a space-occupying lesion was still more probable than the taut distortion one might anticipate in an edema picture. A significant finding, even though not completely appreciated initially, was the relative attenuation of the peripheral vessels.

On 7-31-63, because of some doubt of the angiographic findings, a pneumoencephalogram was done. It showed a marked depression and shift of the incompletely-filled right lateral ventricle (Fig. 4.). Operative findings showed a firm dura, but no increased pressure was found. There was roughening of the dura, and the brain substance was so firm a brain canula could not be passed. The dura was adherent to the brain which was yellow and relatively devoid of vessels. The cortex and subcortical tissues were firm. The white matter was less so. Little bleeding was encountered. The occipital pole was amputated. The ventricular lining was thick and firm. At the close of surgery it was not possible to be certain whether the lesion was tumor or inflammatory.

Pathology:

The meninges were greatly thickened by dense collagen with variable numbers of lymphocytes, plasma cells, histiocytes, and foreign-body giant cells. The latter may be isolated or grouped, usually about a small artery or in its wall associated with fibrinoid necrosis or destroyed elastic fibers. Many of these vessels have lumina obliterated by fibrous tissue and endothelial-cell proliferation. Some of the largest arteries show only elastic lamina reduplication and intimal fibrosis. Careful search with use of specific stains and polarized light failed to reveal any foreign body or organism. Diagnosis: giant cell arteritis.

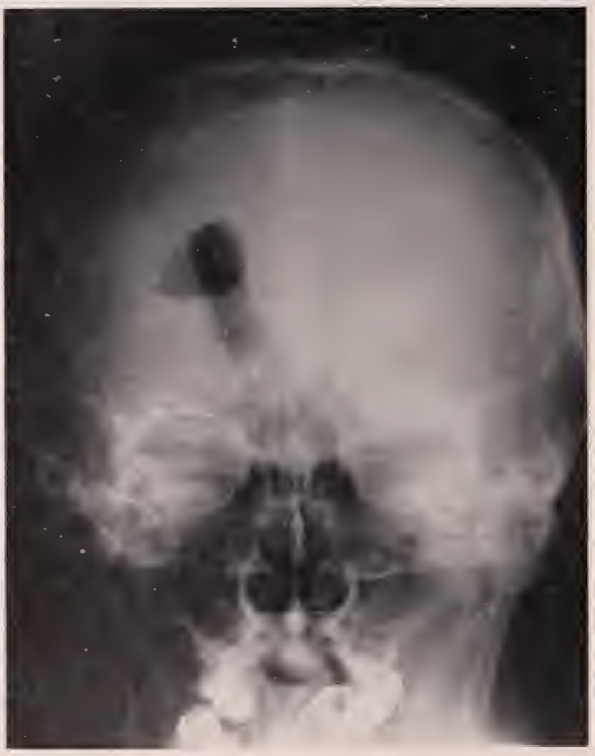

Fig. 4 — Posteroanterior upright of pneumoencephalogram showing shift of left lateral and third ventricle as well as poor fill of the right lateral ventricle with depression and right lateral shift thereof. This finding suggests a space-occupying lesion of the entire right hemisphere.

At the time of writing this report, the patient is alive but, as anticipated, is not doing well.

Discussion

Even though temporal arteritis, a relatively common lesion, histologically resembles the giant cell or granulomatous arteritis of the brain, the latter is extremely rare.[1-6]

Giant cell arteritis of the central nervous system can be best summarized by quoting directly from Budzilovich:[3] "— affects the vessels of the brain predominantly in all cases, and exclusively in most, and is characterized by a granulomatous inflammation involving the adventitia intima or media of many arteries and veins within the central nervous system. The disease is progressive, probably fatal, and constitutes an entity to be distinguished from other forms of vasculitis affecting the systemic vessels. Clinically, the manifestations are entirely neurologic and indicate diffuse disease of the nervous system."

The radiologist must be aware of the entity when he examines an apparent space-occupying lesion which does not display the usual angiographic tumor arborizations, displacements, staining, or characteristic cyst or abscess configuration.

In spite of its involvement of the vascular bed, the contrast visualization of the vessels is not impaired, for the histologic findings are predominantly of the small vessels. Thus the distortion of the vessels is related to the diffuse vasculitis of the small arteries and veins.

The correct diagnosis is not an obvious one from a roentgen standpoint but should probably be considered in the differential diagnosis when correlated with vague clinical and neurological findings developing over a period of months. The angiographic findings suggest an atypical space-occupying lesion with attenuated small vessels while the air studies are more typical for mass. Even though one might anticipate a strong similarity to an edema picture, such was not the case in our findings. Thus it is considered worthwhile to emphasize the point which the author feels should raise the index of suspicion in such a case. That is, one should look for a disproportionately positive air-study finding and a more nondescript narrowing of small vessels on angiography. An isotope scan was not done in this case.

Summary

This report deals with a case of a 67-year-old woman who was found to have a rare lesion, giant cell arteritis of the central nervous system, and this case emphasizes the roentgen diagnosis might be made by exclusion. As described, the findings were somewhat atypical for a classical space-occupying lesion. It is the author's opinion that the unusual nonspecific attenuation of the smaller vessels should bring this entity to mind.

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TURNER'S SYNDROME — (GONADAL DYSGENESIS)

The syndrome of ovarian dysgenesis is manifested typically by infantile development of secondary sex structures, short stature, and multiple congenital anomalies. Commonly associated anomalies are webbed neck, coarctation of the aorta, lymphedema of the extremities and skeletal, ocular and renal defects.

There may be iliac horns, dystrophy of the nails, anomaly of the patellae, and chondrodysplasia and arthrodysplasia, especially of the elbows. The iliac horns are occasionally found in routine roentgenograms and often indicate the presence of other abnormalities. Any one abnormality may occur independently of the others. Less constant abnormalities such as defects of the radial head, prominence of the acromion and clavicle, underdevelopment of the scapula, and discoloration of the iris have been reported.

Transmission occurs as a dominant hereditary character, and study of the genealogic tree of one patient revealed that 30 relatives in four generations exhibited these defects. (Senturia and Senturia).

Secondary sexual development is absent except for sparse pubic and axillary hair. The ovaries are replaced by a fibrotic ridge without evidence of either male or female germinal structures. A chromatin negative (male) sex-chromatin pattern is found in about 80 per cent of such patients. The typical finding in chromatin-negative gonadal dysgenesis is an XO sex chromatin constitution and a chromosome number of 45. In chromatin positive (female) dysgenesis two types of sex-chromatin abnormalities have been described: sex-chromatin mosaicism, and structural anomalies of the X-chromosome. Therapy is directed toward correction of the sexual infantilism and remediable congenital anomalies.

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Sometimes the author's name is more valuable than the manuscript — Print it! — C. O. R.

Hypercalcemia in Malignancy

- without
- Bony
- Metastasis

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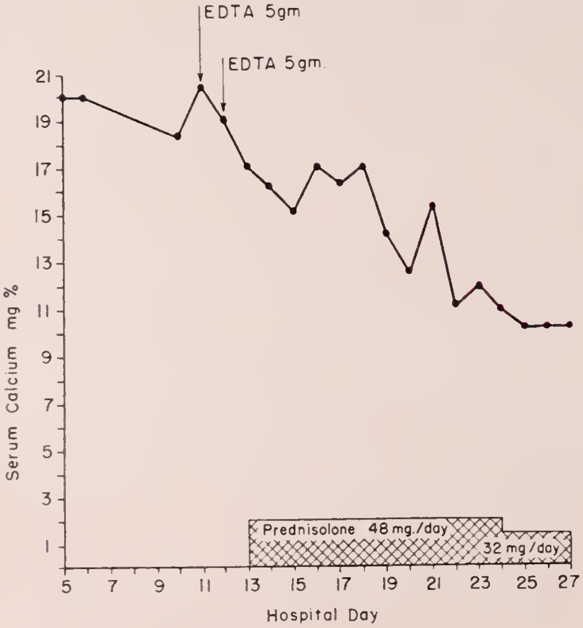

Fig. 1 — F.W., 38-year-old white female with breast carcinoma metastatic to liver. Response of serum calcium to prednisolone therapy.

THE FINDING of an elevated serum calcium level usually suggests the diagnosis of primary hyperparathyroidism to the clinician. Hypercalcemia, however, may be associated with a variety of disorders, among which are Boeck's sarcoid, vitamin D toxicity, hyperthyroidism, fracture immobilization, multiple myeloma, and malignancy. Next to primary hyperparathyroidism, carcinoma with skeletal metastases is probably the most common cause of hypercalcemia. Much less commonly, a malignant neoplasm without bone involvement may produce hypercalcemia. It is important that the clinician be aware of this latter possibility, since frequently other manifestations of the tumor may be obscure and the diagnosis difficult to establish. This form of hypercalcemia can often be controlled with adrenal corticoid therapy, and may disappear with removal of the tumor tissue.

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Recently we had the opportunity to observe and study a patient with marked hypercalcemia secondary to recurrent breast carcinoma without bony metastasis. This report is a summary of our findings and experience in the management of this patient.

Case Report

History:

F. W., a 38-year-old white woman, was admitted to Mt. Sinai Hospital on September 20, 1963, because of drowiness, nausea and vomiting, weakness, constipation, and severe pain in her lower legs. She had felt well until three months before admission when she began to have increasing weakness, thirst, polyuria, constipation, and pain in her legs. During the three weeks prior to admission, she became drowsy and lethargic, with persistent nausea and intermittent vomiting, and increasing leg pain at rest and with activity. She became depressed, emotionally labile, and wept a great deal. There had been a 10-pound weight loss during the three months before admission.

A left radical mastectomy had been performed in 1959 for breast carcinoma. Axillary lymph nodes contained tumor, and surgery was followed by a course of deep X ray to the axilla and the ovaries. She was then started on Premarin®, 1.25 mg. daily. She had felt well and been in apparent good health until June, 1963, shortly after moving to Minneapolis, when her present illness began. Ten weeks before admission, the Premarin was stopped and she received a single injection of 100 mg. depotestosterone. She took an occasional multivitamin preparation containing 1000 units vitamin D, but no other medications. There had been no supplemental calcium intake and she drank very little milk.

Physical Examination

On admission to the hospital, the blood pressure was 142/96 and the pulse 100. The patient was very lethargic and reacted to movement with moaning and weeping. Fundoscopic examination was negative. No masses were palpable in the neck. The left breast was absent and there were well healed scars of a left radical mastectomy and axillary dissection. No masses were palpable in the region of the breast or axilla. The heart and lungs were normal except for a soft systolic murmur heard in the pulmonic area. The liver was palpable 4 cm. below the costal margin and was smooth and nontender. No other abdominal masses were present. There was marked tenderness to motion or palpation of the lower legs over the leg muscles and bones. The color of the legs was normal and there was no edema. The skin and mucous membranes were dry. There was a small amount of hair growth over the cheeks and chin. No other abnormal physical findings were discovered and neurological examination was negative.

Laboratory Studies

Hemoglobin was 12.8 gm% and leukocyte count 8,200 with 63% neutrophiles, 33% lymphocytes, and 4% monocytes. Erythrocyte sedimentation rate was 105 mm/hour. Urinalysis was negative. Fasting blood sugar was 97 mg%, serum cholesterol 202 mg%, sodium 136 mEq/l, potassium 3.7 mEq/l, chlorides 97 mEq/l, CO_2 combining power 28 mEq/l, and blood urea nitrogen 27 mg%. Serum total protein was 6.1 gm% with 3.5 gm% albumin and 2.6 gm% globulin. Serum bilirubin was 0.2 mg., 1 min. and 0.3 mg. total. Thymol turbidity was 2 units and cephalin flocculation negative. Bromsulfalein test revealed 38% retention of dye at 45 min. Prothrombin time was 16.6 seconds with control of 13.6 seconds. A cholecystogram, GI series, barium enema, and bone survey including X rays of the skull, spine, pelvis and extremities were negative. The bone X rays showed no evidence of metastasis or demineralization. A chest X ray was negative. An electrocardiogram was abnormal and revealed multiple ST and T wave changes. A bone-marrow aspiration examination was reported as negative. The 24-hour urinary excretion of 17 ketosteroids was 14.5 mg. and 17 hydroxycorticoids 10 mg. On the fifth hospital day the serum calcium (EDTA chelation method — normal 8.6 — 10.4 mg%) was found to be 20 mg% and the serum phosphorous 4.6 mg%. The serum alkaline phosphatase was 12 K.A. units.

The Influence of Treatment

Serial values of serum calcium are shown in Table 1. (Page 662) The patient was initially treated with limitation of calcium intake and parental fluids to maintain an intake of 3000 ml. daily. By the 11th hospital day the blood ureanitrogen had risen to 68 mg%, serum calcium was still 20 mg%, and the patient was more drowsy and lethargic. Severe leg pain persisted. On the eleventh and twelfth days, sodium versenate (EDTA) 5 gm. was given intravenously. Although the serum calcium level changed only slightly, there was improvement clinically. The patient became more alert and had less nausea and leg pain. On the 13th hospital day, prednisolone 16 mg. every eight hours was begun. The change in serum calcium with treatment is illustrated in Figure 1. The serum calcium gradually decreased and was normal by the 10th day of treatment. Clinically the improvement paralleled the decrease in serum calcium. By the third day of prednisolone therapy, the patient was alert, was no longer nauseated, and had less leg pain. By the eighth day she was able to sit in a chair, feed herself, and walk about the room with help.

On the 18th hospital day (sixth day of prednisolone therapy) a needle biopsy of the liver was performed, and revealed metastatic breast carcinoma in the liver. On the 20th hospital day she was given Cytoxan® 2000 mg. intravenously.

The patient was discharged from the hospital on the 27th hospital day, feeling weak but alert, without nausea, constipation, or leg pain. The prednisolone dosage had been reduced to 32 mg. daily before discharge, and was further reduced to 16 mg. daily two weeks after discharge.

At the time of this report she is taking 16 mg. prednisolone daily, and feeling well except for generalized weakness. The liver is no longer palpable. The serum calcium remains in the normal range and the blood urea nitrogen is 16 mg%. She has received an additional five doses of Cytoxan® intravenously at two to three week intervals, 1000-2000 mg. each dose.

Discussion

Hypercalcemia has been reported to occur in 10 percent of patients with disseminated breast carcinoma and bony metastases, and in 20 percent of those receiving estrogen or testosterone therapy.[1] It has been estimated that bony metastases occur in 50-75 percent of patients with disseminated breast carcinoma.[2] In a review of 699 breast cancer cases, Woodard[3] found hypercalcemia in 18 percent at some time during the course of their disease. Swyer and associates[4] found an elevated serum calcium in 14 percent of 71 patients with breast cancer and bone metastases, seen during a one-year period. In a study of the bone marrows in patients with cancer, Hyman and Harvey[5] found tumor cells in the bone marrows of 10 percent; however, in 37 percent of those with positive marrows there was no X-ray evidence of skeletal metastasis.

Hypercalcemia in patients with localized or disseminated cancer but without skeletal metastases occurs rarely.[6-12] Plimpton and Gellhorn[13] reported 10 patients with malignancy, hypercalcemia, and no bony metastases. The primary tumors were renal carcinoma in four, uterine carcinoma in two, and ovarian carcinoma, bronchogenic carcinoma, Hodgkins disease, and reticulum cell sarcoma in one patient each. In three patients, removal of the primary tumor resulted in a return of the serum calcium level to normal.

TABLE I
F.W. — Calcium balance studies

Hospital Day	Serum Calcium mg%	Serum Phosphorus mg%	Alkaline Phosphatase KA units	Blood Urea Nitrogen mg%	Urine Calcium* mg/24 hr	Therapy
1				27		
5	20	4.6				
6	20		12		257	
10	18					
11	20	5.7		68		EDTA 5 gm I.V.
12	19					EDTA 5 gm I.V.
13	17					Prednisolone 48 mg. daily
14	16		17	62	120	48 mg. daily
15	15				154	48 mg. daily
16	17			49		48 mg. daily
17	16					48 mg. daily
18	17					48 mg. daily
19	14					48 mg. daily
20	12					48 mg. daily
21	15					48 mg. daily
22	11					48 mg. daily
23	10					48 mg. daily
24	10					48 mg. daily 32 mg. daily
25	10					32 mg. daily
26	10					32 mg. daily
27	10				269	32 mg. daily

*Calcium intake 150 mg. daily

In one of these patients the serum calcium again became elevated with recurrence of the tumor. In seven of the patients who came to autopsy, no parathyroid abnormality, bony, or renal lesions could be found. In another two patients, surgical neck exploration revealed normal parathyroid glands.

The cause of hypercalcemia in cancer without skeletal metastases is not known. It has been suggested that the tumor may secrete a humoral substance capable of producing resorption of skeletal calcium and hypercalcemia,[12] or stimulation of the parathyroid glands with resulting hypercalcemia.[14] The remission of hypercalcemia after removal of the tumor tissue, and return of hypercalcemia with tumor recurrence[12,13] would indicate that at least in some cases production of a hypercalcemia substance by the tumor does occur. The parathyroid glands have been found to be normal,[4,13,15] making it unlikely that the hypercalcemia is produced through parathyroid gland hyperfunction. Patients with cancer are often inactive or immobilized because of weakness, cachexia, or pain, and this may play a role in the elevation of serum calcium.

We have included our patient in the category of cases with cancer, spontaneous hypercalcemia, and no bony metastases, based on the absence of evidence of skeletal involvement during the four-month period of observation. It is possible that bony metastases are present but not visible on X ray; but this would seem unlikely in view of the length of time involved. She had received estrogen and testosterone before the hypercalcemia was recognized; however, it is unlikely that this was a factor, since there was a 10-week interval between the last estrogen or testosterone administration and the finding of a markedly elevated serum calcium. The control of hypercalcemia of this type by adrenal corticosteroids was well illustrated in our case. The early treatment of these patients will depend on the ability of the clinician to recognize the syndrome of hypercalcemia. It is probably advisable to check the serum calcium periodically in all patients with incurable and disseminated malignancy.

Summary

A patient with extreme hypercalcemia and disseminated breast carcinoma without bony metastases has been presented.

The elevated serum calcium returned promptly to normal and has remained normal with prednisolone therapy.

The importance of prompt recognition of the syndrome of hypercalcemia and its early treatment in patients with neoplastic disease has been emphasized.

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Oath & Prayer of a Doctor

O, grant —
That neither greed for gain, nor thirst for fame, nor vain ambition,
May interfere with my activity.
For these I know are enemies of truth and love of men,
And might beguile one in by profession
From furthering the welfare of Thy creatures.
O strengthen me.
Grant energy unto both body and the soul
That I might e'er unhindered ready be
To mitigate the woes,
Sustain and help
The rich and poor, the good and bad, enemy and friend.
O let me e'er behold in the afflicted and suffering,
Only the human being.

Moses Maimonides (1135-1204) was a physician, rabbi and author. Born in Spain, he spent most of his life in Egypt where he was physician to the Sultan. Among his works are many theological, philosophical and medical treatises.

Max A. Shapiro,
Rabbi, Temple Israel, Minneapolis

IT'S THE LAW

Fee Splitting does not Make Referring Physician Liable for Surgeon's Negligence — A physician who shared offices and equipment with a surgeon was not liable for the surgeon's negligent treatment of a patient referred to him by the physician's office, even though the two doctors had an arrangement whereby they divided the fees whenever either treated the other's patients. Reversing a lower court ruling, an intermediate appellate court in New York held that there was no liability, since the physician, who was ill, took no part in the care or treatment of the patient and there was no written partnership agreement between the doctors. Any irregularity which might appear with respect to the fee spliting should be dealt with by disciplinary action, rather than by imposing vicarious liability, the court said.

Graddy v. New York Medical College, 243 N.Y.S. 2d 940 (N. Y., Nov. 7, 1963).

Take Time TO PRAY — It is the greatest power on earth.

Hemodynamic Studies of the Left Heart*

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IN CORRECTIVE surgery for acquired or congenital heart disease, physiologic studies of the left heart have become necessary in the evaluation of the patient. Cardiac catheterization and angiography have made it possible to estimate the degree and magnitude of the suspected defect. The following case reports illustrate how such studies aided in the diagnosis and future management.

Case No. 1 Mitral Stenosis

E. S., a 48-year-old female, was told at the age of 21 during a routine physical examination that a cardiac murmur was present. A diagnosis of rheumatic heart disease with mitral stenosis was established two years prior to the time of study. Because of increasing weakness, dyspnea, and fatigue, as well as objective evidence by X ray of increasing pulmonary congestion, it was elected to evaluate the patient for possible mitral commissurotomy.

The electrocardiogram revealed a sinus rhythm with evidence of right ventricular preponderance. Cardiac fluoroscopy showed moderate overall cardiac enlargement with left atrial enlargement and prominent pulmonary vasculature. Kerley's lines were noted at the costophrenic sulci bilaterally. No intracardiac calcification was noted.

Right-heart catheterization was carried out and the resting pulmonary artery pressure was noted to be 80/30 mm.Hq. Pulmonary artery wedge pressure was 35 mm.mercury. This represents an integrated mean pressure. Trans-septal catheterization of the left atrium[2] with a Ross needle was carried out, and direct left atrial pressure was 45/30 mm.Hq. A left ventricular pressure was determined by retrograde catheterization of the aorta using the method of percutaneous puncture of the femoral artery. The catheter was passed through the aortic valve and into the left ventricle. This pressure was 102/4 mm. Hq. (Figure 1)

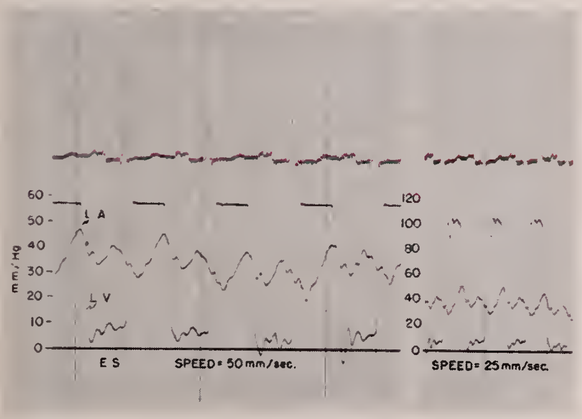

Fig. 1 — (Case 1) The curve demonstrates an elevated diastolic pressure gradient across the mitral valve. There is no evidence of regurgitation. At operation the valve opening was 0.6 cm^2. LA = left atrium LV = left ventricle.

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*Supported in part by the Mount Sinai Hospital Women's Auxiliary.

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The calculated mitral valve area by use of Gorlin's hydraulic formula was 0.63 cm^2. The normal valve area of the mitral valve is from 4 to 6 cm^2. The calculated pulmonary vascular resistance was 263.8 dynes/second/cm^{-5} which is about two and one-half times normal.

Based on this objective evidence of a significant mitral valve block, a closed mitral commissurotomy was carried out. The valve opening at the time of surgery was found to be the same as the calculated valve opening. The patient made an uneventful recovery from surgery and is clinically much improved

Comment

This patient was studied to elucidate the degree of mitral block.[1] Clinically there was little evidence of progression of symptoms but objective signs by X ray and electrocardiogram were suggestive of significant mitral block. The subjective symptoms of dyspnea and fatigue are difficult to evaluate, and it is necessary to document evidence for mitral block if any degree of success is to be attained by mitral commissurotomy. There are three conditions benefitted by objective studies. The first is that of patients with numerous subjective symptoms without evidence of high degree of mitral block. These will not be candidates for surgery. The second group of patients on whom objective clinical data is helpful are those with a low degree of mitral block but with diffuse myocardial involvement. These patients' findings are manifested by a low cardiac output and only slightly increased pulmonary artery pressures. The third is that group with pulmonary disease and mitral stenosis. It is necessary to know the degree of mitral block to evaluate the significance of the clinically diagnosed mitral stenosis.

Case No. 2 Silent Mitral Incompetence

M. S., a 26-year-old married female, was admitted to Mount Sinai Hospital with a history of known heart murmur since the age of 13. She had been asymptomatic all along and admission was done for the purpose of evaluation. She had a questionable history of rheumatic fever at age six.

Examination revealed a blood pressure of 150/80 mm. of Hg., a pulse of 80 per minute and regular. The heart was not enlarged to percussion; the rhythm was regular. A systolic thrill was palpable over the precordium, and a grade IV/VI murmur was heard along the left sternal border. The pulmonary second sound was not accentuated.

The electrocardiogram was consistent with left ventricular hypertrophy. Cardiac fluoroscopy and films, however, were not suggestive of any abnormality, and there was no evidence of any individual chamber enlargement. (Figure 2a)

The clinical impression of interventricular septal defect had been suggested by the above findings, and in order to assess the degree of possible shunting the patient was evaluated by right-heart catheterization. This study was somewhat surprising in that no shunt was found, and right heart pressures were normal. Left-heart catheterization was then done through percutaneous puncture of the left femoral artery (Seldinger method), and a #260 polyethylene catheter advanced into the left ventricle. Pressures were normal and

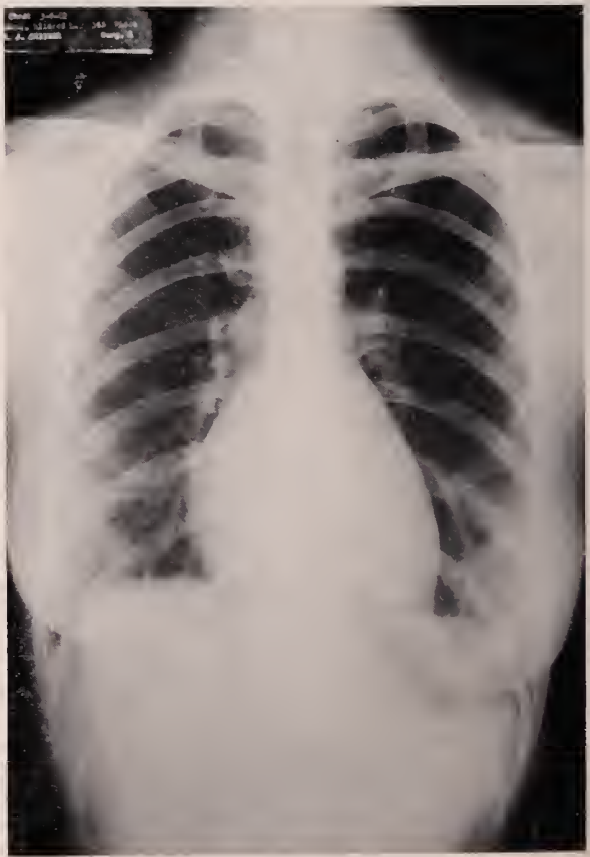

Fig. 2a — (Case 2) The chest roentgenogram portrays the overall cardiac size as within normal limits. There is slight prominence of the outflow tract of the right ventricle and main pulmonary artery. There is no definite left atrial enlargement.

no evidence of aortic valvular disease was found. Left ventriculogram with the injection of 35 cc. of 75% Hypaque® into the left ventricle was then done to demonstrate possibility of a small left to right shunt, and immediate regurgitant filling of left atrium was noted, demonstrating instead a grade IV mitral insufficiency. (Figure 2b)

Comment

The unusual location of the murmur and the absence of left atrial enlargement suggest the syndrome of "silent mitral incompetence."[3]

The location of the murmur in mitral insufficiency is believed to be related to the direction of flow of the regurgitant jet of blood through the incompetent valve.[4] In case of incompetence of the posterior mitral leaflet, the ausculatory findings may be located in the topographic aortic or upper sternal area, as in this patient, where angiographic study was essential in establishing a diagnosis.

Case No. 3 Aortic Stenosis

I. W., a 50-year-old male electrician, had a history of progressive shortness of breath, angina and syncope for 15 months. There was no history of rheumatic fever. A murmur was noted one year prior to onset of symptoms.

On physical examination the blood pressure was 104/84 mm.Hg. The heart was not enlarged. There was a systolic thrill felt at the base, and a grade V/VI diamond-shaped systolic murmur heard at the base and transmitted to the left sternal border, apex and carotid vessels. The aortic second sound was absent. There was a grade I/VI decrescendo diastolic murmur at the base. Peripheral pulses were diminished in intensity.

Cardiac fluoroscopy showed minimal left ventricular enlargement, aortic dilatation with slight prominence of pulsation. (Figure 3a)

Calcium deposition was noted in the annulus of the aortic valve. An electrocardiograph was consistent with left ventricular strain.

Right-heart catheterization demonstrated normal pressures and absence of left to right shunt. Simultaneous pressure tracings of the left ventricle and the central aorta revealed a gradient of 125 mm. of Hg. pressure across the aortic valve (Figure 4). The calculated aortic valve area was 0.47 cm^2 (normal valve area is 3.0-4.0 cm^2). The cardiac output was calculated as 3.84 liters per minute (Fick principle). The central selective aortogram demonstrated ectasia of the ascending limb of the aorta, widely patent coronary arteries, mild aortic insufficiency, and a deformed bicuspid aortic valve (Figure 3b) obtained by percutaneous catheterization of the left ventricular cavity and aorta.

Comment

Catheterization of the left ventricle and aorta confirmed the clinical impression of aortic stenosis. The gradient across the aortic valve must be correlated with the cardiac output and end diastolic pressure. As

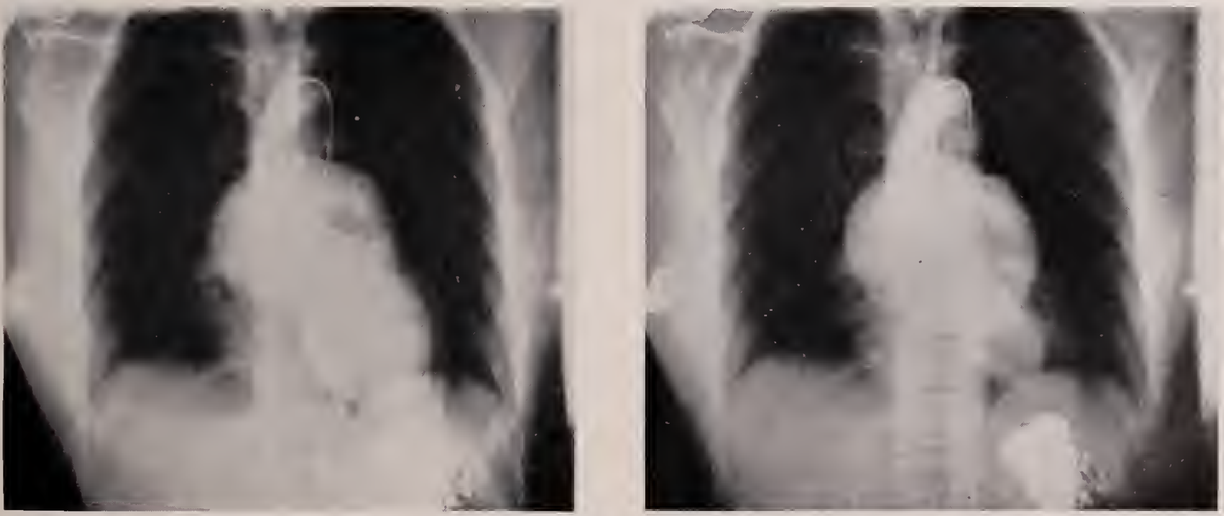

Fig. 2b — The left ventriculogram indicates simultaneous filling of the left atrium and left ventricle, more prominent during ventricular systole.

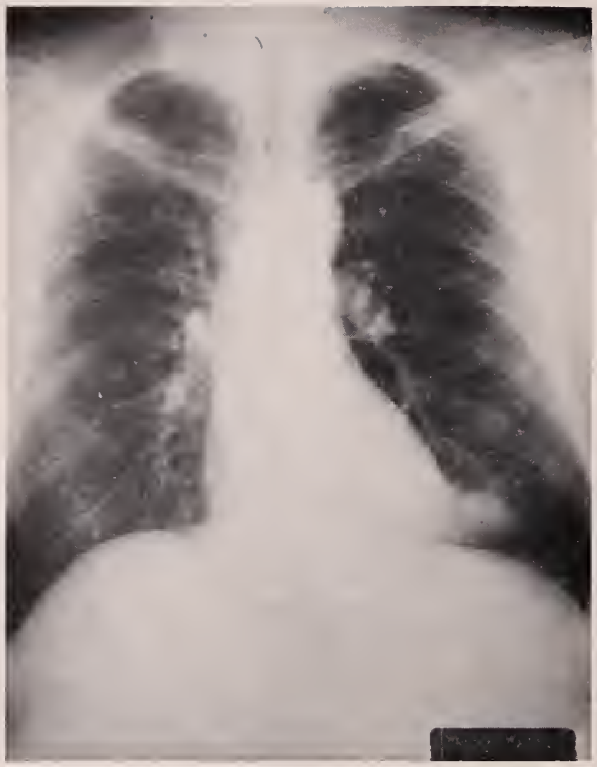

Fig. 3a — (Case 3) Chest roentgenogram demonstrates minimal left ventricular hypertrophy. On fluoroscopy, calcification is noted in the annulus of the aortic valve.

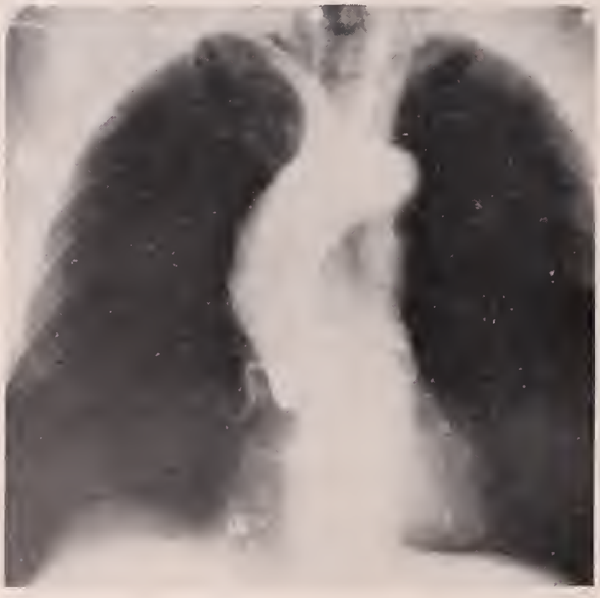

Fig. 3b — Retrograde aortogram portrays ectasia of the ascending limb of the aorta and widely patent right and left coronary arteries. Irregularity of the aortic valve and minimal aortic regurgitation are also demonstrated.

myocardial failure ensues, cardiac output falls, pressure gradient falls, and ventricular end diastolic pressure increases.[5,6] The aortogram was helpful to the surgeon in that the size of the annulus was visualized; and secondly, the coronary vessels were shown to be patent, eliminating the possibility of gross coronary arterial block.

The catheterization and angiographic findings were all confirmed in surgery.

Case No. 4 Outflow Tract Obstruction

L. H., a 54-year-old farmer, was evaluated for easy fatigue and syncopal-like attacks. These attacks occurred on exertion and symptoms had been present for approximately six months. A cardiac murmur had been noted since early childhood but there was no history of rheumatic fever and no family history of cardiac disease. Physical examination revealed a blood pressure of 110/70 and a grade III/VI ejection type murmur at the base and left sternal border. The aortic second sound was greater than the pulmonic second sound.

Electrocardiogram revealed a normal axis and amplitude with diffuse ST and T-wave changes in limb and precordial leads consistent with myocardial ischemia. Cardiac fluoroscopy revealed left ventricular enlargement without evidence for intracardiac calcification. (Figure 5a)

Right-heart catheterization revealed no evidence of left to right shunt and the pulmonary artery pressure was within normal limits. There was no gradient of pressure across the pulmonic valve. The cardiac output, calculated by the Fick principle, was 3.2 liters/minute. Left-heart catheterization was accomplished by percutaneous femoral artery method. Pressure in the left main ventricular cavity was 118/8. Pressure in the left ventricular outflow tract was 94/10, and in the root of the aorta 102/85. A ventriculogram was carried out, as shown in Figure 5b. This study indicated an infundibular stenosis with a bicuspid aortic valve. The subvalvular muscular stenotic zone is approximately one inch in length. (Figure 5b)

Comment

This case illustrates very well the need for complete study in patients presenting with symptoms and signs of outflow tract obstruction. On physical examination this patient presented the classical signs of outflow tract obstruction. The differential diagnosis included rheumatic valvular obstruction of the aortic valve, congenital valvular or subvalvular obstruction, and primary myocardial disease. The long history of cardiac murmur and the presence of a clear aortic second sound suggested the possibility of congenital subvalvular stenosis. The pressure determinations with a change in pressure in the outflow tract and a small gradient of pressure across the aortic valves is suggestive of this diagnosis; however, confirmation was established by ventriculogram. The absence of a valvular component and a small gradient of pressure across the aortic valve dictated a course of medical rather than surgical treatment at this particular time. Good results from surgery have been reported in subvalvular obstruction of a membranous type where a diaphragm-like structure is found in the subvalvular area. In cases with primarily muscular hypertrophy of the outflow tract the reports have been less favorable.[5] This study was thus crucial for the complete elucidation of the diagnosis as well as outlining the course to be followed in the future.

Case No. 5 Atrioventricularis Communis

R. M., a 15-month-old white male, had cardiac catheterization because of a congenital heart lesion. A tracheoesophageal fistula had been successfully repaired shortly after birth. A systolic precordial murmur was noted at this time, and later an apical diastolic murmur. The heart gradually enlarged and the child developed signs of cardiac failure. Although the decompensation responded to medical treatment, the child failed to grow and thrive normally. He remained hyperpneic but was not cyanotic.

Serial chest roentgenograms and cardiac fluoroscopy confirmed the cardiac enlargement. (Figure 6a)

Pulmonary vasculature markings indicated a left to right shunt but no enlargement of the left atrium. Repeated electrocardiograms revealed left axis deviation, first degree heart block, and right ventricular hypertrophy.

The presumptive clinical diagnosis was atrioventricularis communis.

Cardiac catheterization was performed through the right saphenous vein. Pulmonary hypertension, a left to right shunt in the atrium and also in the ventricle were demonstrated as the abnormal hemodynamic findings.[7,8] The catheter could also be easily passed into the left ventricle through the defect. A selective left ventriculogram

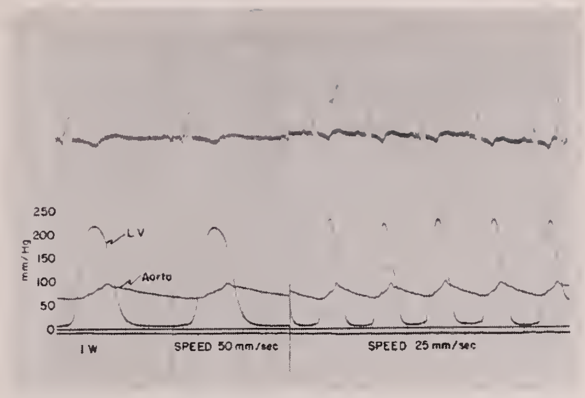

Fig. 4 — (Case 3) Simultaneous pressure tracing portrays the marked left ventricular-aortic gradient. An aortic valvular opening of 0.3 cm^2 was found in surgery.

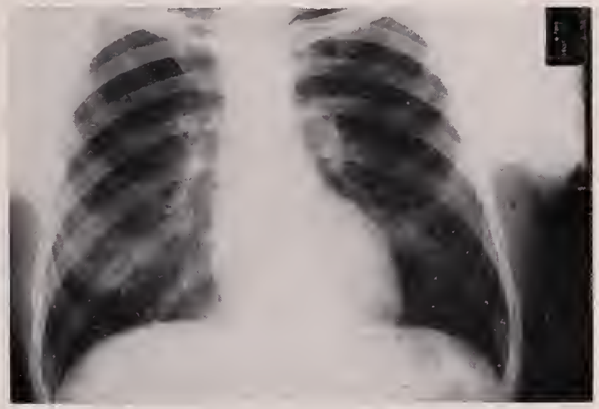

Fig. 5a — (Case 4) Posteroanterior roentgenogram: there is an enlarged heart with prominent left ventricular hypertrophy, and uncoiling and ectasia of the aorta.

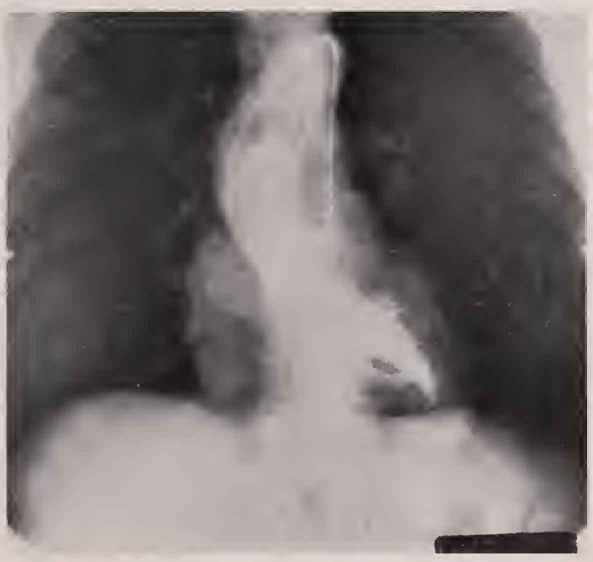

Fig. 5b — Left ventriculogram demonstrates the small left ventricular cavity even in diastole, subvalvular stenotic zone and bicuspid aortic valve.

through this catheter demonstrated a diagnostic sign of atrioventricular communis. (Figure 6b)

Comment

Cardiac catheterization and left ventricular angiogram were necessary to determine the severity of the congenital heart defect as related to the extent of derangement of intracardiac architecture and pulmonary pressure changes.

The left ventricular angiogram demonstrated the radiographic finding diagnostic of an atrioventricularis communis. This is the corrugated outline of the left superior border of the intraventricular septum which results from the insertion of abnormal, chordae tendinae attached to the deformed common atrialventricular valve (i.e., the precursors of the tricuspid and mitral valves). There was also reflux of contrast into the right atrium and right ventricle through the septal defects, which further confirms the diagnosis. The curved position of the catheter is also abnormal.

Access to the left heart through a patent foramen ovale, atrial septal defect or, as in this case, a common atrioventricular valve, is often possible by passing a catheter through a peripheral vein into the right heart. As the catheter enters the right atrium via the inferior vena cava, the catheter lies in the same plane as the foramen ovale. If the valve is not fused at the borders, the catheter may traverse the valve and enter the left heart chambers. This is possible in many adults and most infants and allows study of the left heart without arterial catheterization in some patients with intact atrial septa, as well as in those with defective septa.

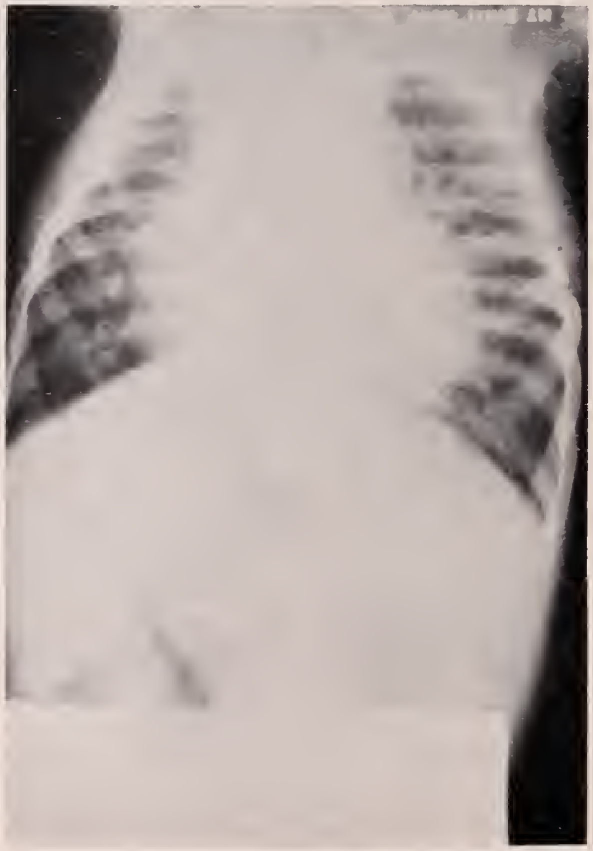

Fig. 6a — (Case 5) Chest roentgenogram outlines the cardiomegaly and prominence of the pulmonary vasculature consistent with left to right shunt.

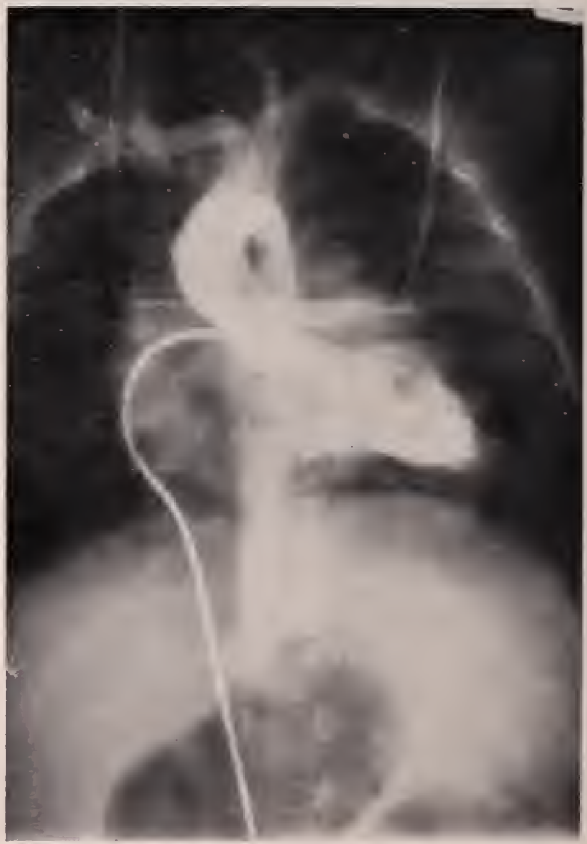

Fig. 6b — Left ventriculogram outlines the corrugated appearance of the left superior border of the interventricular septum. There was also reflux of dye into the right atrium and right ventricle demonstrated. This is pathognomic of atrioventricular canal.

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The Health of Louis XIV

Louis XIV, the Grand Monarch . . . "was the healthiest ruler in Europe in his day, and under his guidance France rose to that position of elegance to which her capital still lays claim. In spite of his unusual health and vigor, Louis had a few of the diseases natural to his time. By present-day standards, even with these few diseases he would be judged as distinctly a pathological specimen.

He started out at birth with two teeth, so we are told, and much to the worriment of his wet-nurse. He had smallpox when he was nine, and a few years later a venereal infection. He had typhoid fever before he was twenty, and when he was twenty-five he contracted measles from the queen. He had a tapeworm. His teeth decayed and became abscessed — he had pyorrhea, and no tooth-brush. At forty-four he developed gout, and in the following year he dislocated his elbow in a fall from his horse. Three years later he developed a most personal, but unmentionable complaint, that interfered considerably with his royal magnificence, and for a time he did not sit upon the throne. He was cured by surgical treatment. Incidentally the surgery of his time was in ill-repute, and the royal recourse to this art served to rehabilitate it. Next the king acquired malaria from the mosquitoes which rose in swarms over his favorite carp pond. The king took quinine, newly introduced from South America. He was cured, and his recovery popularized the use of quinine. Later he had a serious carbuncle, his gout grew worse, and he developed hardening of the arteries. The king soon thereafter died of these natural causes."*

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*Haggard, Howard W., M.D.: "The Lame, the Halt, and the Blind," p. 397.

Stork: a bird with many things charged against it which should have been blamed on the lark. — Jacob Braude's "Speaker's Encyclopedia"

It is necessary and normal for the young person to disown his parents in order to find himself. — Edward J. Harnick, M.D.

Gross Chromosomal Abnormality

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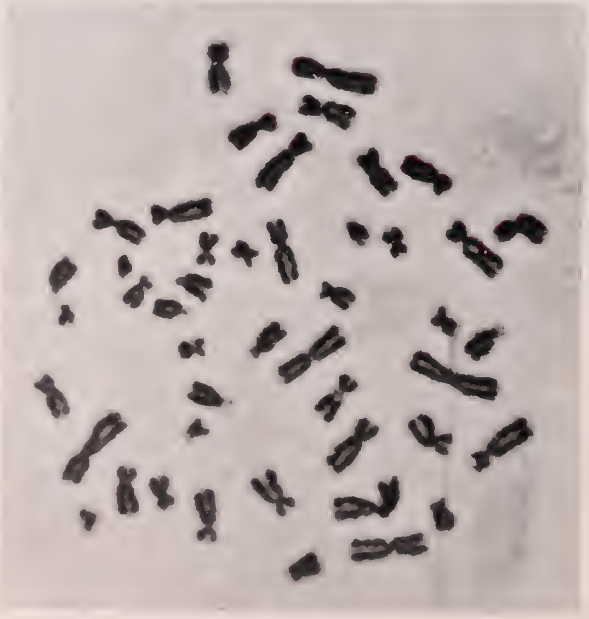

Fig. 1 — Chromosomal spread from white cell of peripheral blood.

THE LABORATORY determination of an abnormal chromosome complement is difficult, time-consuming, and hence, expensive! It is, therefore, incumbent upon the physician to consider carefully this fact before ordering that such a procedure be carried out on a patient who has an array of signs that "don't seem to fit." To employ the procedure as a screen, moreover, is unfair, even if the patient can afford the procedure, since most laboratories which conduct the test are connected with educational institutions, engaged in research of their own and are flooded with more requests to test "highly suspicious" patients than they can handle.

What then makes a patient highly suspicious? What less expensive tests should we employ first if we suspect an X-chromosome abnormality? What should characterize the patient's history to make one carry out further chromosomal or other investigations? These are a few of the points we should like to consider in making our decision whether to request a chromosome analysis.

Known Chromosomal Syndromes

Autosomal Trisomy

At this writing, three chief examples of

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Clinical and Laboratory Aids in the Diagnosis

autosomal trisomy, i.e., the presence of three rather than a pair of corresponding chromosomes have been extremely well documented: Trisomy 13-15 (or D trisomy); Trisomy 18 (or E syndrome), and Trisomy 21 (or Down's syndrome or G syndrome). Each has a characteristic clinical picture.[7,8,9,10,14]

Syndromes

In addition there are eight or more syndromes known to involve either extra X or Y chromosomes or the elimination of one of the X chromosomes.[3-6] It would be foolhardy to predict that no more will be found, but it is safe to hazard a guess that many new translocation and partial trisomy syndromes will be described within the next decade.

Clinical Picture of Chromosome Syndromes

The medical practitioner is most familiar with the clinical picture of the most common (about 1 in 500 births) of the autosomal chromosome syndromes — Trisomy 21 or Down's syndrome (the term Mongolism should be discouraged). He may be somewhat less familiar with two of the sex chromosome syndromes, i.e., Turner's (XO) and Klinefelter's (XXY) syndromes. The other syndromes are less well known. Let us review in abbreviated form (Table 1) and familiarize ourselves with some of the more

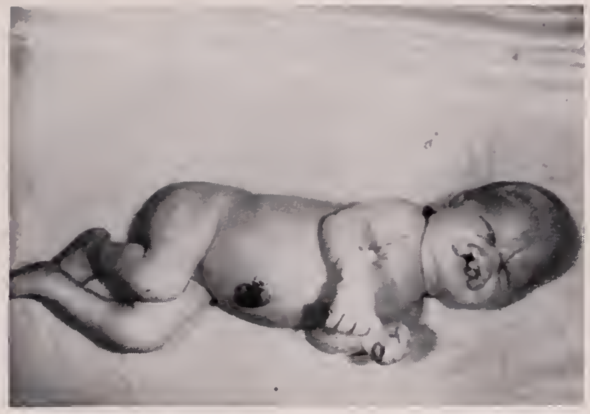

Fig. 2 — Trisomy 13-15 or D syndrome. Note anophthalmia, bilateral cleft lip-palate, ulnar hexadactyly, umbilical hernia. Patient also had congenital heart defect.

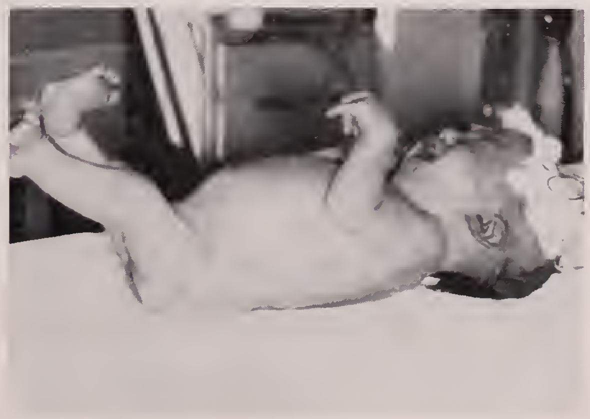

Fig. 3 — Trisomy 18. Infant was markedly cyanotic, hypertonic. subject to seizures. Note talipes equinovarus, elfin ear, small mandible.

common signs of these symptom complexes.

Finger, Palm and Foot Prints

In the case of a suspected chromosomal anomaly, familiarity with dermatoglyphics may be of significant value. However, like nearly all laboratory tests, dermatoglyphics have limitations. Patients having trisomy for chromosomes 13-15, 18, 21 and XXXXY syndromes have characteristic finger, palm, or plantar patterns, and a few hours of study and practice should make the practitioner familiar with them. The precise nature of the abnormalities is beyond the scope of this paper, but the reader is referred to the excellent concise articles of Uchida et al.,[11] Penrose,[12] and Uchida and Soltan.[13]

Buccal Scraping

The buccal scraping is easily performed with a tongue blade, smearing the exfoliated cells on a clean slide and fixing in a 50-50 alcohol-ether mixture. After appropriate staining, (the easiest is aceto-orcein) the buccal epithelial cells are examined under oil immersion.

The technique is of value only if an abnormality (increase or decrease) in the number of X chromosomes is suspected. It is of no value in ascertainment of an abnormality of autosomes or of the Y chromosome.

The technique provides an estimate of the number of X chromosomes present by counting the number of cells having nuclear membrane chromatin clumps (Barr bodies). Since the Barr body represents the tightly coiled X chromosome, there should be one less body than the number of X chromosomes. For example, the normal female, being XX, has one Barr body visible in about 25 per cent of exfoliated cells (chromatin positive), while the normal male, being XY, has none (chromatin negative). In the case of XO individuals (Turner's syndrome) there is likewise none (unless the patient is a mosaic, i.e., has more than one stem line of cells). Patients having XXY (Klinefelter's syndrome) would have one Barr body (chromatin positive); and XXX and XXXY patients would have two of these nuclear membrane masses in some of the cells. The rare patient with an XXXX or XXXXY pattern would exhibit three Barr bodies, etc.

Family Pedigree Analysis

Family History of Anomalies

In most patients with multiple congenital anomalies, no family history will be obtained. However, if, upon questioning, it is revealed that other individuals in the family have or have had similar anomalies, a thorough pedigree analysis should be undertaken.

Conditions which are exhibited and transmitted from parent to offspring through several generations (dominant inheritance) are *not* those which are prone to exhibit gross chromosomal anomalies!

No Family History of Anomalies

Now what about the isolated case, i.e., one having normal parents? This may be "pay dirt," since most patients with gross chromosomal abnormalities are isolated cases. However, the physician should be aware that he may be dealing with a new mutation of a dominant trait or more likely a recessive trait. Recessive inheritance, by definition, is expressed only in individuals carrying two doses of the abnormal gene. Each parent, carrying only one of the genes, is ostensibly normal, though subtle biochemical changes may often be detected. What then would cause us to suspect that we are dealing with a recessively inherited trait? If the family is large, since each sibling has a one in four chance of being affected, there may be more than one individual with the same condition.

Consanguinity of the parents of a child affected by an unusual condition would suggest recessive inheritance. Individuals related by blood tend to share more genes than do random individuals. In general, the rarer the recessive condition, the higher the per cent of patients with a history of a consanguinous marriage somewhere in the patient's antecedents.

If we are dealing with an X-linked recessive trait, i.e., one which is carried by females and transmitted to male offspring, the

TABLE I

Trisomy 13-15	Trisomy 18
1. Mental retardation	1. Mental retardation
2. Apparent deafness	2. Moderate hypertonicity
3. Apneic spells and seizures	3. Failure to thrive
4. Bilateral sloping forehead	4. Flexion of fingers
5. Microphthalmia and/or colobomas	5. Low-set, malformed ears
6. Ear malformations	6. Micrognathia
7. Cleft lip and cleft palate	7. Meckel's diverticulum
8. Hemangiomas	8. Dorsiflexion of hallux
9. Cardiac defects	9. Short sternum
10. Polydactyly	10. Patent ductus arteriosus
11. Horizontal palmar creases, etc.	11. Hernia: inguinal, umbilical, diaphragmatic
12. Hyperconvex, narrow fingernails	12. Talipes equinovarus, rocker bottom feet
13. Multiple genitourinary anomalies (septate uterus, cryptorchidism)	13. Corneal opacity
14. Characteristic dermatoglyphics	14. Small placenta
	15. Polyhydramnios
	16. Finger prints — arches
Trisomy 21	**XO Syndrome**
1. Incidence: 1 in 500 births	1. Incidence: 1 in 3000 female births
2. Mental retardation	2. Primary amenorrhea
3. Short stature	3. Pterygium colli
4. Brachycephalic, flat occiput	4. Micrognathia
5. Slanted, wide spread eyes	5. Short stature
6. Epicanthus, strabismus, nystagmus	6. Low posterior hairline
7. Short neck	7. Narrow high-arched palate
8. Broad flat hand, clinodactyly	8. Congenital lymphedema of extremities
9. Gap between great and second toe	9. Cubitus valgus
10. Characteristic dermatoglyphics	10. Broad chest, wide-spaced nipples
	11. Clinodactyly
	12. Abnormal fingernails
	13. Coarctation of aorta
	14. Renal anomalies
XXX and XXXX Syndromes	**XXY Syndrome**
1. Incidence: ca. 1 in 250 instit. females or in 1 in 700 female births	1. Incidence: 1 in 300 male births
2. Mental retardation — I.Q. ca. 30	2. Normal penis, small testes
3. Internal strabismus	3. Aspermatogenesis
4. Father 40 years or over	4. Variable gynecomastia
	5. Elevated urinary gonadotropins
	6. Asocial behavior
XXYY, XXXY and XXXXY Syndromes	
1. Incidence: 1 in 2000-4000 inst. ment. retarded males	7. Prognathism, heavy brow
2. Mental retardation (I.Q. 20-50)	8. Small frontal sinus
3. Penile size greatly reduced, scrotum rudimentary	9. Cleft palate
4. Radio-ulnar synostosis, patellar dislocation	10. Clinodactyly — 5th finger
5. Lordosis, scoliosis, coxa valga	11. Varicose veins, acrocyanosis
6. Strabismus	12. XXXXY syndrome — dermatoglyphics (arches common)
	13. Hyposegmentation of neutrophils

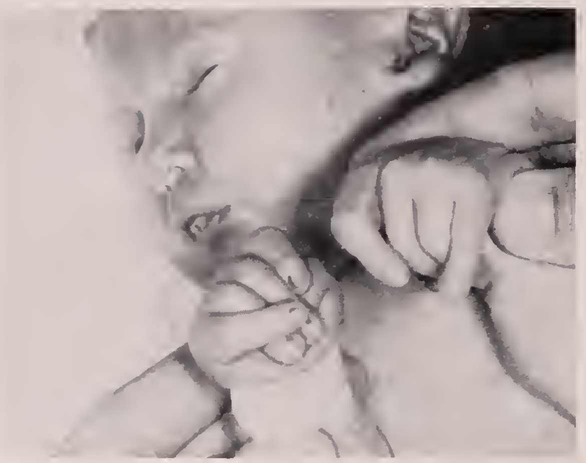

Fig. 4 — Trisomy 18. Note ptosis and digital anomalies.

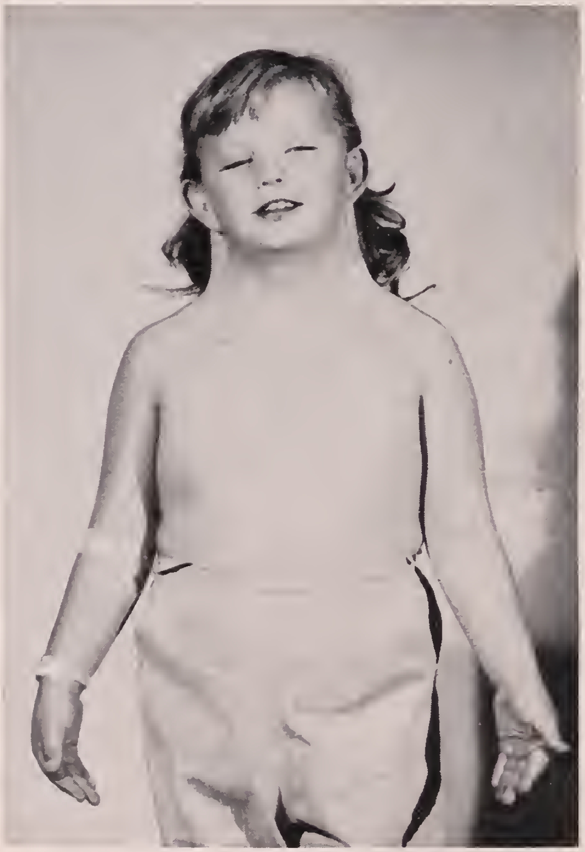

Fig. 5 — Turner (XO) syndrome. Short child with marked pterygium colli, hypoplastic, wide-spaced nipples, mild cubitus valgus, small mandible.

trait may appear to be sporadic since the families may have tended to be small and there may have been a chance occurrence of all female children. Often, however, the condition will appear in the affected individual's brothers or mother's brother (50 per cent risk), the sons of the mother's sisters (25 per cent risk), or in the mother's father (50 per cent risk).

The isolated case may also be the result of a dominant gene in which the penetrance is poor, thus "skipping" a generation. Further, we may be dealing with a case of illegitimacy, or, in possibly the majority of cases, the condition may not be of hereditary nature. Conversely, "familial cases" are not necessarily hereditary, for example, endemic cretinism.

Should every child with Trisomy 21 or Down's syndrome have his karotype determined? I do not believe so, as the vast majority are of the conventional nondisjunction type. If, however, the mother is young and she has had two such children, the chromosomal status of the children and both their parents should be determined. In the cases of a translocation between chromosomes 15 and 21 or 21 and 22, the chances for a second affected child with Down's syndrome are one in three if the mother is a carrier and appreciably less (possibly one in 20), for reasons unknown, if the father carries the translocation.

Environmental Factors

A thorough gestational history should be conducted to try to rule out environmental factors. However, in most cases this is fruitless. Numerous known, and a whole host of unknown, factors may affect the developing embryo producing a phenocopy or environmentally-produced pathologic condition which mimics a known hereditary state.

Teratogenic Agents

The most recent tragic example of teratogenic agents is the thalidomide debacle. The number of teratogenic agents experimentally employed in animals is legion. In humans, intrauterine radiation, cytotoxic drugs and infection of the fetus by toxoplasmosis may all induce gross congenital anomalies; but these are rare.

History of Repeated Miscarriages

Patients having reciprocal translocation of chromosomes commonly exhibit a history of multiple miscarriages. Moreover, it has recently been demonstrated that about 25 per cent of embryos, aborted prior to the eighth intrauterine week, had a chromosomal anomaly including Trisomy D, Trisomy E, Trisomy G, Turner's syndrome and triploidy.[2] The frequency of spontaneous abortion in first pregnancies is about 10 per cent (range of 6-17 per cent in several surveys) rising to about 40 per cent if the patient has already had two previous abortions. The risk increases to over 80 per cent if the patient has had three spontaneous abortions. Because the risk is not markedly increased after one (less than 15 per cent), perhaps a history of three miscarriages should be minimal warranty.[1] It should be borne in mind, however, that a chromosomal anomaly is not a common cause of spontaneous abortion, especially if it is after the eighth intrauterine week!

Parental Age

In general, children with gross chromosomal abnormalities are born to older parents, though this is not true in the case of Turner's syndrome. (See Page 659) Mothers of 20 years of age have about one chance in 2,000 of having a child with Trisomy 21, while mothers conceiving at 45 years of age have a one in 50 chance of having such a child.

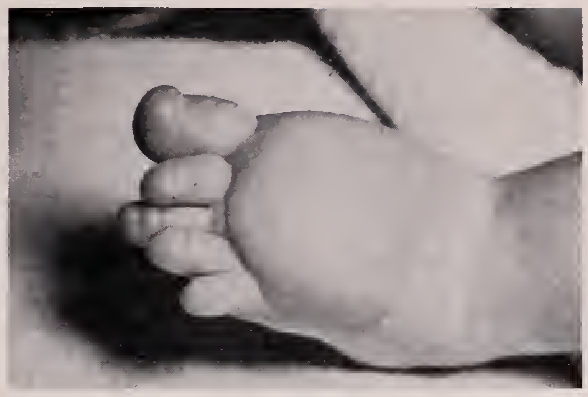

Fig. 6 — Turner (XO) syndrome. Lymphangiectatic edema of extremities common in this syndrome in infants.

Parents of advanced age, therefore, would increase the suspicion.

Summary

The author explores the factors to be considered in determining whether a patient should have a chromosome analysis for detection of a gross chromosomal anomaly. These include: (a) signs and symptoms exhibited in known chromosomal syndromes, (b) abnormal dermatoglyphics, (c) abnormal numbers or size of Barr bodies on buccal scraping, (d) unusual pedigree analysis, (e) history of repeated miscarriages, (f) advanced parental age, etc.

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DOWN'S SYNDROME

In 1866, J. Langdon Down, an English physician, attempted to classify his countrymen with mental retardation by their ethnic features. Those with negroid characteristics he classified as Ethiopian mental deficients. Other patients he examined resembled Malayans and some were similar to American Indians. One group of very similar patients had certain oriental features and he labelled these mongols. The Ethiopian, Malayan, and North American Indian classification have long been forgotten but the mongoloid category is well known and is occasionally referred to as Down's Syndrome.

This syndrome is a common cause of mental retardation being found in one to two out of every thousand newborns and 10-15% of institutionalized mental defectives. Most, but not all of these patients are born to mothers over thirty-five years of age. Usually cases are sporadic, but occasionally more than one may occur in a family.

Typical associated features include hypotonicity of the muscles, widespread eyes, epicanthal folds, oblique palpebral fissures, a flattened acetabular angle, a short crooked finger with only one flexion fold, short broad hands, abdominal distention, a furrowed tongue, high arched palate, strabismus, nystagmus, and a flat occiput. When coupled with short stature, protruding tonge and open mouth, the habitus and facies of the mongoloid child are often quite characteristic. Even the fingerprint pattern is typical.

Longevity is diminished by the high frequency of congenital heart lesions (septal and a-v canal defects), duodenal stenosis, frequent pulmonary infections, and leukemia.

Mongolism was the first syndrome to be associated with a chromosomal abnormality. Most mongols have forty-seven chromosomes, although some of those that are familial have the normal number of forty-six. Even these, however, have a chromosome defect.

While mongolism was first described in Englishmen, it has subsequently been noted in all races around the world. In the oriental it may be somewhat more difficult to diagnosis, but there is no dearth of mongolian mongoloids!

ANSWER TO WHAT'S YOUR DIAGNOSIS

(From page 655)

Postoperative atelectasis in the finer radicals of the right lower lobe secondary to the deep anesthesia, shallow respirations, and inability to cough. The major bronchi are open. This explains the findings that mimic pneumonia.

Eugenics

Men are not going to embrace eugenics. They are going to embrace the first likely, trim-figured girl with limpid eyes and flashing teeth who comes along, in spite of the fact that her germ plasm is probably reeking with hypertension, cancer, haemophilia, color-blindness, hay fever, epilepsy, and amytrophic lateral sclerosis.
— Logan Clendening

Too Much Truth

Our senses can grasp nothing that is extreme. Too much noise deafens us; too much light blinds us; too far or too near prevents our seeing; too long or short is beyond our understanding; too much truth stuns us. — Blaise Pascal

Microsurgery

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RECENT ADVANCES in operative techniques, together with such adjuncts as extracorporeal circulation and hypothermia, have made extensive operative manipulation of crucial small vessels, such as the coronary and middle cerebral arteries, a distinct possibility. Therefore, the recent upsurge of interest in various improved methods of anastomosis of small vessels, measuring less than 4 mm. in external diameter, is certainly well justified. The efforts of many investigators to perfect a rapid and dependable anastomotic technique, yielding a satisfactory long-term patency rate, has already led to the development of several promising techniques, although their rare application to the human indicates that certain technical difficulties are yet to be surmounted.

Interest in small vessel anastomoses is not a recent development. As early as 1909 Alexis Carrel performed an anastomosis between the popliteal vein of a three-day-old infant and the radial artery of his father for blood transfusion purposes,[1] as well as numerous other anastomoses on equally small vessels in various organ-transplantation experiments. Although occasional reports on this subject have appeared in the literature over the last 15 years, it is only during the past three years that an intensive study of this problem has been undertaken.

These research efforts have followed two main avenues of investigation: the development of suture and nonsuture techniques suitable for small vessel anastomoses. At the present time equally satisfactory results have been reported by the most succesful proponents of both methods. In all likelihood they will both play an important role in microvascular surgery, the choice between them being determined by the equipment available, the location of the vessels operated upon and the experience of the surgeon.

Suture Technique

Jassinowski[2] reported the first successful suture anastomosis in 1889; but with the possible exception of the investigations of Carrel[3,4] and Guthrie[5] around the turn of the century, no significant studies on small vessel anastomoses were published until 1948, when Shumacker and Lowenberg[6] reported discouraging results from their investigations on various anastomotic methods for

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small vessels. On the other hand Seidenberg and his co-workers[7] (1958) reported satisfactory although not well-defined results on vessels ranging from 1.5 to 4 mm. in diameter. They applied their techniques successfully in the replacement of the human cervical esophagus by free jejunal autotransplants, a procedure requiring the anastomosis of the inferior thyroid artery to the radial artery of the jejunal segment, measuring 2.5 mm. in diameter.

Jacobson and Suarez[8] (1960) believed that earlier failures were due primarily to the employment of gross techniques clearly incompatible with the minute size of these vessels. They felt that vision provided by the naked eye was inadequate for the suitable preparation of the vessel ends (removal of the adventitia) as well as for proper placement of the sutures. They attempted to improve the results of previous investigators by performing the anastomoses under an operating microscope and introducing a number of new instruments specifically designed for the micromanipulative needs of their technique. They were eminently successful, reporting 100% patency of 54 anastomoses on vessels measuring 1.4 to 4 mm. in diameter followed for periods up to four months. Chase and Schwartz[9] (1962) were not convinced that specialized equipment was essential for the successful performance of small vessel anastomoses. They reported excellent results using a binocular loupe providing only a four-power magnification. Although all their anastomoses, performed on vessels 1.2 to 1.7mm. in diameter, were patent after 14 days, various degrees of thrombosis were present in 26% of them.

Nonsuture Technique

Early attempts at nonsuture vascular anastomoses date back to the work of Abbe[10] (1894) and Queirolo[11] (1895) who employed an intravascular glass tube to unite blood-vessel ends. Nitze[12] (1897) used an ivory cuff for the same purpose and Payr[13] (1900) described a method of vascular union over an extravascular magnesium ring, later modified by the use of two connectors that could be coapted by means of pins and corresponding holes. This type of approach has been used anew by Holt[14] (1960) and Nakayama[15] (1962) with great success. Tuffier[16] (1915) suggested the use of intravascular silver tubes for the temporary restoration of the continuity of severed blood vessels.

More recently Blakemore[17] (1942) used vitallium tubes, lined with an autogenous vein graft for the reconstruction of traumatic arterial defects. However, the studies of Johns[18] (1947) indicated that Blakemore's method was probably inferior to direct suture techniques. Extravascular prostheses such as tantalum tubes, polyethylene tubing and stainless steel rings have been employed for nonsuture anastomosis with variable success. Urschel and Roth,[19] using stainless steel rings, reported a 95% patency of 85 anastomoses on vessels varying from 1.75 to 4 mm. in diameter, observed for periods up to two years.

Holt and Lewis[14] (1960) modified a technique already described by Payr[13] in 1900 and achieved 100% patency of 18 anastomoses on vessels varying from 1.5 to 2.5 mm. in diameter, observed for periods up to six months. Their method involved the use of two teflon rings, bearing stainless steel pins alternating with holes placed in a manner permitting complete coaptation of the two rings, the pins of one fitting into the holes of the other after passing through the everted ends of the vessels.

Several mechanical vessel-suturing instruments have been described in the literature. Androsov[20] (Soviet Union, 1956) was the first to report on an instrument designed for vessels ranging from 1.3 to 15 mm. in diameter. He has not, as yet, presented the patency rate of small vessels on long-term follow-up. Inokuchi[21] (Japan, 1958) designed a similar instrument but has not reported the minimum vessel size on which this tool can be applied. Vogelfanger[22] (Canada, 1962), using his mechanical device on vessels 2 to 3 mm. in diameter, achieved a 70% patency rate on both arteries and veins. Finally Nakayama[15] (Japan, 1962), describing the use of the simplest of these devices, based on a principle similar to the one used by Holt and Lewis, reported an 86% patency of internal mammary-coronary anastomoses in the dog (1.5 to 2.5 mm. in external diameter) for periods of observation exceeding six months.

More recently the use of tissue adhesives has been introduced as an aid to the performance of small vessel anastomoses. Carton et al.[23] (1960) studied the use of methyl-2-cyanoacrylate for the fixation of vessel ends over a stainless steel ring. Hafner et al.[24] (1963) used the same material for direct vascular union. Both groups of investigators reported a 50% incidence of thrombosis (Table 1, Page 684).

Jacobson Technique and Its Applications

Jacobson and his co-workers[8], in their belief that the failure of previous investigators to achieve satisfactory long-term patency rates of small vessel anastomoses was due to the employment of techniques incompatible with the size of these vessels, described a refined suture technique applicable to vascular structures measuring less than 5 mm. in diameter.

They performed their vascular suturing under an operating microscope which allows a more complete removal of the adventitia and a more accurate placement of the stitches. They introduced specially designed miniaturized instruments, including spring-type needle holders and scissors. In order to stabilize the anastomotic and arteriotomy sites in the field of the microscope they designed a universal arm that could be attached to a pair of serrefine vessel clamps and placed in any desired position. A vernier screw device between the two serrefine clamps allowed adjustment of the distance between them and consequently of the tension on the anastomotic site. The suture material most commonly used by these authors was 7-0 silk swaged onto a fine atraumatic needle. However, some finer suture material (8-0 monofilament nylon) swaged onto the smallest needle available was also developed under their direction. It certainly offers distinct advantages when the vessels approach a size of 1 mm. in external diameter or when lymphatics are sutured. This technique was applied by Jacobson and his co-workers to the suture anastomoses of several small tubular structures. Their results were most satisfactory in the case of arterial replacement by autogenous and homologous grafts. There was not a single case of occlusion among 54 such replacements on vessels measuring 1.4 to 4 mm. in diameter. In addition this technique was applied with variable degrees of success to the reconstruction and anastomosis of veins, lymphatics, nerves, ureters, bile ducts, Fallopian tubes and vasa deferentia of experimental animals.[25]

A recent investigation of this technique in our laboratory has essentially confirmed the validity of its principles. Five arteriotomy closures, measuring 1.5 to 3 cm. in length, and performed on vessels measuring 1 to 2 mm. in external diameter were found to be completely free of thrombosis 50 to 109 days after the operation. Nine out of 12 anastomoses, performed on vessels 1.1 to 3 mm. in external diameter, were completely patent five to 180 days after the operation. One was partially open 69 days after the operation and two were occluded.

These procedures were carried out on femoral and brachial arteries of small mongrel dogs. Employment of this technique allowed the application of five to six stitches per millimeter on the suture lines; 7-0 silk was primarily used but 8-0 monofilament nylon was also employed in some instances. The latter allowed the performance of finer anastomoses, but its relative rigidity and its almost microscopic size rendered its manipulation somewhat difficult.

In addition, this technique was used in patch angioplasties on canine femoral arteries, measuring 2.5 to 4 mm. in diameter. The prosthetic material employed for these procedures consisted of a loose-mesh teflon matrix coated by a continuous sheet of silicone rubber. The patches measured 2.5 to 3 cm. in length and about 0.5 cm. in width. Six out of 10 arteries were found to be occluded at the site of the angioplasty within a month after the operation. The rest remained completely patent for periods of observation up to six months (Fig. 1). It was felt that this high rate of occlusion was due to the nonporous nature of the prosthetic material rather than to inadequacy of the microsurgical technique.

Description of New Instruments and Modified Microsurgical Technique

Although this technique yielded satisfactory results, it soon became apparent that the available instruments and equipment imposed certain undesirable limitations on the accuracy and rapidity of suturing under the operating microscope. The greatest difficulty was presented by the Jacobson needle holder (a modification of the Castroviejo type), which is still designed to be manipulated by the palm of the hand but is difficult to manipulate with the fingers. In order to execute ultrafine movements the hand is probably best placed in the position of writing with the forearm well supported and motions basically limited to the thumb, index and middle fingers.

Needle Holder

Therefore, in order to satisfy these requirements, a needle holder was designed that could be manipulated like a writing tool, having its jaws activated pneumatically and controlled by a foot pedal. Under these circumstances no exaggerated motions are required for suturing and, furthermore, the number of motions necessary for placing each stitch is reduced.[26]

Figure 2 is a drawing of the pneumatic needle holder. A schematic diagram of the mechanism employed for the activation of the jaws can be seen in the upper portion of the same figure. When pressure from a source of compressed gas is applied on the piston (P), its wedge action closes the dual lever jaws. When the pressure is released, a stainless steel spring (S) returns the piston to its previous position and the jaws open.

The total length of the needle holder is approximately seven inches and its diameter approximately $\frac{3}{8}$ inch. The external jaws are smooth and measure $\frac{1}{2}$ inch in length. Their tips are approximately 1 mm. wide and 3 mm. apart when open.

Compressed Air Mechanism

Compressed air is transmitted to the piston from a polyethylene tube (P.E. 260) which is light enough not to interfere with the manipulation of the needle holder. The polyethylene tubing is attached to a foot valve mechanism (Fig. 3) which consists of a commercially available three-way air valve and essential pedal components. Application of pressure by the foot on the metal pad moves the actuator lever to its open position, allowing compressed air to enter the needle holder and close the jaws. When the pressure is released, two springs return the lever to its closed position interrupting the inflow of compressed air and allowing it to escape from the needle holder portion of the circuit. The

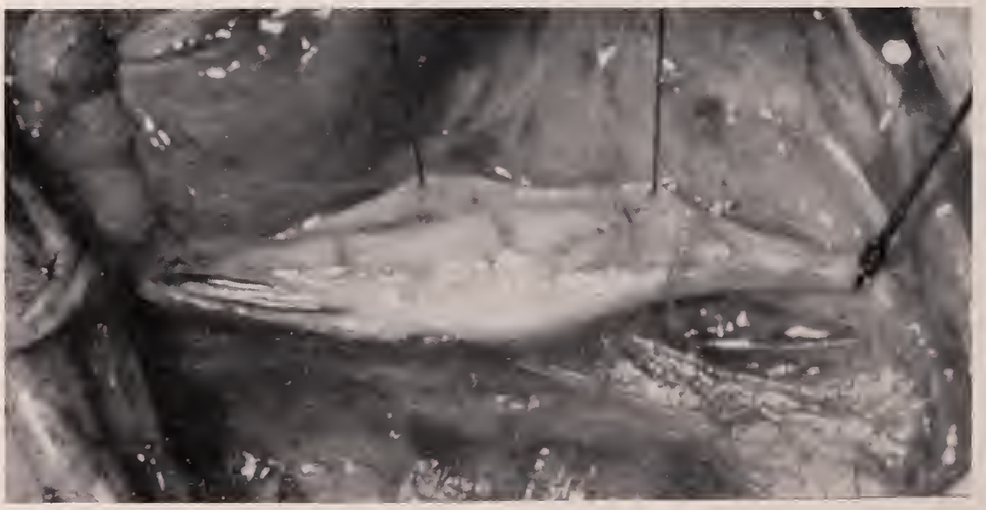

Fig. 1 — Silastic patch angioplasty of canine femoral artery, measuring 2.5 mm. in external diameter, performed according to the Jacobson technique. Note patency six months after operation.

jaws are then returned to their open position by the stainless steel spring.

Since operating rooms are seldom, if ever, provided with compressed air outlets, tanks of compressed oxygen, nitrogen or carbon dioxide may be used as the source of pressure. A satisfactory pressure reduction can be obtained by using a pressure regulator. It has been found that a line pressure of 50 psi will result in a holding force more than adequate for manipulation of the smallest needle attached to 7-0 silk. This instrument has been used quite extensively in our laboratory for the performance of small vessel anastomoses and in the operating room for venolymphatic anastomoses. Our experience with it has been quite gratifying. In our hands it allows vascular suturing under the operating microscope to proceed at twice the speed afforded by other needle holders.

Vascular Clamp

In connection with the problem of stabilization of the vessels in the field of the microscope it appeared necessary that three essential requirements be met by whatever apparatus is used: (1) The clamp applied directly on the vessels should not crush or damage their wall, and its dimensions and construction should be compatible with the small size of these structures. (2) Any parts of the apparatus positioned in the vicinity of the suture line should be small and unobtrusive enough not to interfere with the operative manipulations of the vessel. (3) The instrument should be easily placed in whatever location is found necessary to allow accurate and variable positioning of the vessel ends during the performance of the anastomosis.

It was felt that the serrefine arrangement originally proposed in association with this technique did not meet all of the above requirements to a satisfactory extent. Serrefine clamps, although widely used in general vascular surgery, present certain inherent disadvantages which render them almost inadequate for small vessel surgery. They are by no means atraumatic to the smaller vascular structures, particularly lymphatics; the pressure with which they are applied can hardly

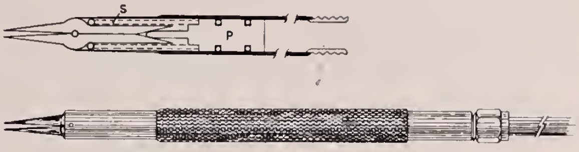

Fig. 2 — Drawing of the pneumatic needle holder. Insert illustrates cam-operated mechanism used for activation of the jaws. P: piston. S: spring. See text for further details.

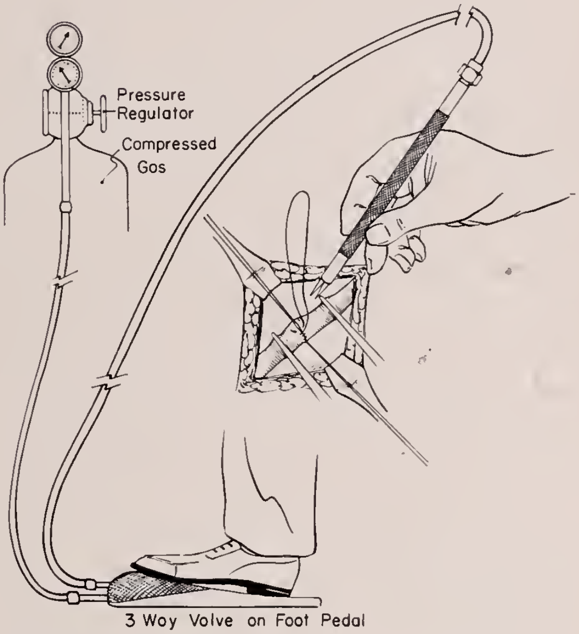

Fig. 3 — Equipment necessary for operation of the pneumatic needle holder: tank of compressed gas, pressure regulator and foot pedal.

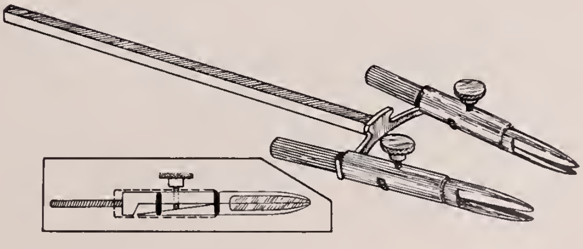

Fig. 4 — Atraumatic vascular clamp used for stabilization of vessel ends. Insert illustrates mechanism used for regulation of the pressure applied on the vessel by the clamp.

TABLE I
Microsurgery

(A) Suture Technique

Authors	Year	Country	External Vessel Diameter	Description of Method	Experimental Results	Application
1. Alexis Carrel	1909	U.S.A.	?	3 Stay Suture Technique	Good	Transplantation of Organs. Radial Art. of Donor to Popliteal V. of Infant for Transfusion.
2. Schumacker and Lowenberg	1948	U.S.A.	Less Than 4 mm.	Several Suture Techniques	Poor	
3. Seidenberg et al.	1958	U.S.A.	1.5-4.0 mm.	Continuous Over & Over Suture (7-0 Silk)	Good	Free Jejunal Autograft for Replacement of Esophagus
4. Jacobson and Suarez	1960	U.S.A.	1.4-4-0 mm.	Use of 7-0 Silk, Special Instruments & Operating Scope	100% Patency	
5. Chase and Schwartz	1962	U.S.A.	1.2-1.7 mm.	Use of Magnifying Loupe Only	74% Patency	
6. Salmon and Assimacopoulos	1963	U.S.A.	1.0-3.0 mm.	Use of Pneumatic Needle Holder	88% Patency	

Microsurgery

(B) Nonsuture Technique

Authors	Year	Country	External Vessel Diameter	Description of Method	Experimental Results	Application
1. Androsov	1956	U.S.S.R.	?	Automatic Suturing Device		Free Jejunal Autografts for Replacement of Esophagus
2. Urschell and Roth	1958	U.S.A.	1.75-4.0 mm.	Stainless Steel Rings	95% Patency	
3. Inokuchi	1958	Japan		Automatic Suturing Device		
4. Holt and Lewis	1960	U.S.A.	1.5-2.5 mm.	Two Teflon Rings with Pins and Holes	100% Patency	
5. Carton et al.	1960	U.S.A.		Stainless Steel Rings & Tissue Adhesive (Methyl-2-Cyanoacrylate)	50% Patency	
6. Vogelfanger et al.	1962	Canada	2.0-3.0 mm.	Automatic Suturing Device	70% Patency	
7. Nakayama	1962	Japan	1.5-2.5 mm.	Automatic Suturing Device	85% Patency	Free Colonic Autografts for Esophageal Replacement
8. Hafner et al.	1963	U.S.A.		Direct Vascular Union with Tissue Adhesive (Methyl-2-Cyanoacrylate)	50% Patency	

Table 1 — Historical review of suture and nonsuture methods for small vessel surgery.

be controlled; and their vertical height may often impede comfortable access to the suture line, unless an inordinate length of the vessel end is dissected free. In addition the Jacobson vernier screw device with which the two serrefine clamps are connected allows regulation of their relative distance only, but does not permit any rotation of the vessel ends. However, upward rotation of the vessel lumen would render the placement of the initial stay sutures, probably the most time-consuming step in the performance of the microanastomosis, easier and less traumatic to the vessel, since no other instrument but the clamp would be required to hold the vessel in place.

Figure 4 illustrates the vessel holder designed to meet the requirements previously outlined. Its hexagonal stem is 5 inches long and can be attached to the Jacobson universal arm. Each clamp measures 2½ inches in length, can be placed at any point along each side arm (¾ inch), and can be rotated around its long axis by any desired angle. The jaws of the vascular clamps measure 2 cm. in length and approximately 2 mm. in width. The maximum opening between the tips is 3 mm. The jaws can be brought together by turning the screws on top of the clamp. The construction of the instrument is such that the jaws of the clamp will close down to a certain point and then open again so that the vessel will never be excessively compressed. Before the clamp is applied, a thin sheet of ivalon sponge is wrapped around the vessel in order to protect it and provide sufficient friction to avoid slipping. The pressure required to occlude and hold the vessel securely in place can be adequately regulated by the screw attached to the clamp. If properly applied this instrument will leave no signs of its presence even on the most delicate vessel.

Technique

A strictly aseptic and atraumatic operative technique should be stringently followed during microvascular procedures if good results are to be obtained. Any trauma to the intima in particular should be completely avoided. The operator should be comfortably seated with his forearms well supported so that fatigue and motion are minimized.

The adventitia of the vessels to be anastomosed is carefully and completely excised, a procedure carried out under the operating microscope. The lumen of the vessel is irrigated with heparinized saline by means of a 22 gauge blunt needle and any thrombotic material removed. A thin sheet of compressed ivalon sponge is wrapped around the vessel end and tied loosely in place. The clamp is then applied over the ivalon sponge so that a 2 to 3 mm. segment of the vessel end is free.

With the vessel lumina turned upwards two or three stay sutures are placed and the vessel ends brought together. The long ends of the stay suture are weighted by means of mosquito forceps, in order to stretch the anastomotic line, while the short ends are used for suturing. The needle should enter the wall of the vessel at such a distance from its end that it can still be seen through the tissue. Five to six stitches per millimeter are placed on the suture line (Fig. 5).

The needle holder is held like a pencil by the first three fingers and all rotational and manipulative motions required for suturing are performed by the finger tips. The grip of the needle holder is adequate enough to

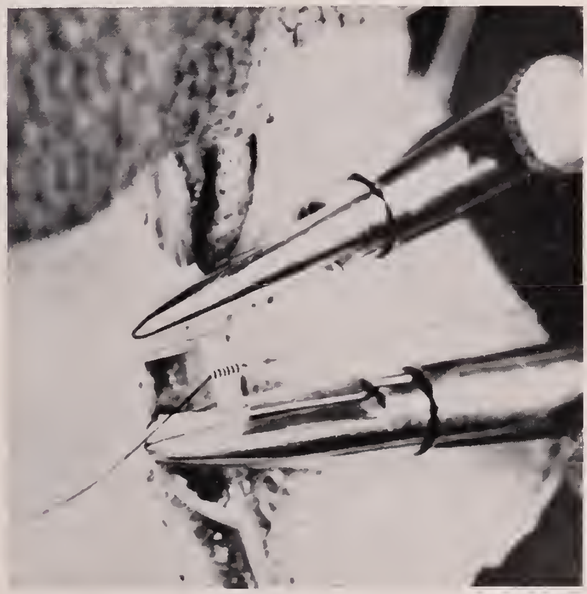

Fig. 5 — Vascular clamp in use during the performance of an anastomosis on vessel measuring 2 mm. in external diameter.

allow tying instrument knots even with the finest suture material.

Efficiency in suturing is greatly increased if the needle is manipulated effectively without need for frequent repositioning and if the suture is kept relatively short (3 to 4 cm. in length). Under these circumstances all manipulations can be performed within the field of the microscope. Otherwise much time and effort may be wasted in searching for loose needles and suture ends placed outside the field.

The combined use of the pneumatic needle holder and the vascular clamp described above has been found to facilitate and expedite considerably any procedures carried out under the operating microscope. In our hands the pneumatic needle holder allows microsuturing to proceed at twice the speed afforded by other needle holders. In addition the vascular clamp permits minimal manipulation of the vessel ends, unimpeded access to the anastomotic site and avoidance of any trauma to the vascular wall.

Summary

The literature on small vessel surgery is reviewed and the major trends in suture and nonsuture techniques outlined. Two new adjuncts to microsuture techniques are described: a pneumatic needle holder and an atraumatic double vascular clamp. A detailed account of their use in the performance of microanastomoses is given.

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19-26 Will appear in the reprints or can be obtained from the author.

Something is true, not because it has been repeated often; not because some one in authority has said it; not because it has been deduced from an infallible generality; but because it leads as accurately as possible to the kind of result that we have in mind. — William James

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America is a willingness of the heart. — Scott Fitzgerald

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*Donnelly, J.: A.M.A. Arch. Environmental Health 6:697, June, 1963

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Editorials

High Standards: Teaching and Research*

WHAT ARE the high standards we seek and how far have we progressed in achieving these standards? As the merchants say, let's take stock. To some people, a hospital is rated only in terms of the physical structure or the elegance of its appointments and furnishings. These, of course, are desirable. More important in a hospital, however, is whether it is giving continuous intensive medical care throughout 24 hours of each day.

Is it enough to operate a hospital with physical facilities but without an alert and ever-present house staff? Mt. Sinai has established a teaching program with full-time directors of surgery and medicine, with residents in major services, and with teaching of interns and externs. Imagine the catastrophe of a sudden attack experienced by a hospital patient at a time when the attending physician is at his office or making house calls — or, if you will pardon the frankness, out fishing or playing golf. Doctors are only human. But those are the intervals when the quality of care of the patient is measured principally by the quality of the house staff. High standards of hospital care are synonymous with high standards in the resident staff.

One of our greatest jobs in the near future will be to educate the public generally to the meaning of a teaching and research program, and to the superior medical advantage to the patient of a permanent house staff.

---

*Excerpt from an address by Mr. Jay Phillips, President of Mt. Sinai Hospital Board of Governors given at the annual hospital meeting May 1963.

House Staff in a Private Hospital

MOST HOSPITALS want a house staff. In these days of two positions for every applicant for internship or residency every hospital's desire in this matter can not be fulfilled. In this buyers' market a private hospital trying to sell a house staff program might well consider the following basic conditions that should be fulfilled before such a program can be undertaken with any hope of success.

1. A Director of Medical Education must

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be hired and he should be employed full time at the hospital. Everyone or nearly everyone on the staff must take part in the teaching program. But the great task of co-ordination and direction should not be entrusted to anyone who might subordinate this task to someone else. Such a full-time man may and should have other duties in the hospital. He should be involved in his own and other research programs, but his prime assignment must be to direct medical education.

2. The preponderant majority of the medical staff must co-operate with the teaching program. They must take part in the exercises and meetings, make ward rounds with the house staff, and do their stint of formal lecturing. Staff co-operation need not be 100 percent; in a democratic society there must be room for the critics, the it-won't-workers. Their number changes reciprocally with the success of the program.

3. There must be a fund for providing beds for medically indigent who will be treated by the resident staff as their primary physicians under the supervision of the medical director with assistance from the attending staff. In a two-hundred-bed medical and surgical service such as at Mt. Sinai in Minneapolis, twenty beds are available for this purpose. These are not necessarily "free" beds. Many patients admitted to the teaching services are able to pay part of the hospital cost. The lay board and administration should realize that the service patient must have at least an equal chance with the private patient to get a bed when the hospital is crowded. Every member of the house staff must be given an opportunity to have his own service.

4. The preponderant majority of the private patients must accept their responsibility in a teaching program: to allow themselves to be the subjects of ward rounds and clinics. Here too, not everyone must be made to fit this mold, but the responsible leaders in the community should set the example. Every patient entering the hospital should be informed of his privilege in being admitted to a hospital with a house staff and of his responsibility toward physicians in training.

5. The teaching program must teach. Undoubtedly the house staff learns from such exercises as doing histories and physicals, starting intravenous injections, and visiting nonsleepers at night. But when these chores are laid on excessively, the effect becomes immediately obvious at the end of the training year: the discommendations of the current house staff dry up the replacement pool. About four hours of activities must be planned for the house staff every day, including formal rounds, informal rounds with staff men on their own patients, conferences, and lectures. On final analysis, in the small hospital with a small staff and a great task to be done, success depends upon the enthusiastic help of the medical staff. And naturally the staff shares in the benefits that accrue to the hospital able and willing to undertake such a program.

Reuben Berman, M.D.
Minneapolis, Minn.

Obesity: A Medical Therapeutic Challenge

FRUSTRATING, difficult, disappointing, usually unsuccessful are the terms most commonly used in describing the treatment of obesity. Obtaining results from therapy is as difficult as the diagnosis is easy.

Importance

This nation has an epidemic of overnutrition. Obesity adversely affects vascular diseases, diabetes, arthritis, gout, gallbladder disease, pulmonary function, surgical risks, etc. The literature is full of references documenting the hazards of obesity. The majority of deaths in the country today are caused by diseases usually complicated by obesity. In view of this, insurance companies have demonstrated the adverse affect of obesity on longevity.

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Dosage: Usual dosage is 1 or 2 tablets 4 times daily.

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Methods of Therapy

One can no longer give the patient stereotyped management with a routine diet. There probably are as many ways to treat these patients as there are patients to treat.

It is now believed that patients respond differently to caloric intake according to their "metabolic behaviour." The management of each patient is an individual problem, just as the management of the diabetic is an individual problem.

Reducing regimens vary from 1500 calories daily to intermittent starvation. The number of calories necessary to sustain life and physical health varies in different individuals, and also in these same individuals with age. For example, there is a continuously decreasing need for calories in the older age groups, thus forcing an increasingly difficult periodic adjustment.

Obviously, the number of calories necessary to sustain life and physical health — which can be surprisingly small — are not the same as the amount needed to satisfy hunger or appetite. This is the crux of the situation. The physician needs the greatest ingenuity to cope with these varying demands. Again, the problem is probably best handled on an individual basis. For example, some patients cannot tolerate the boredom of 1,000 calories daily but are very content and successful on 7,000 calories per week. There is considerable difference in the two diets, since the latter allows much more latitude. This probably is the main point of the starvation routine. In addition to showing rapid, encouraging results, it allows more liberal diets between periods of starvation. I believe there is little difference between the two total caloric intakes if plotted over a long period of time. It remains to be proven, however, which type of management will be most successful over long-term observation. That is, "steady-state" diets versus short-term fasting versus long-term fasting. Perhaps this is an individual matter and even varying combinations of all types will be used at appropriate intervals.

Drugs are useful periodic adjuncts. However, the less they are used, the better. They are helpful when the patient is at an impasse and needs a breakthrough. Metabolic stimulants like triiodothyronine, anorexic agents, and diuretics are helpful.

Psychotherapy is mandatory. Simple support, guidance through stressful periods, proper timing of "crash" programs, encouragement and understanding should be given by the physician. If there is a suggestion of a complex emotional problem, psychiatric consultation should be obtained.

Results of Therapy

The results depend on: (1) the severity of the disease, (2) the intelligence of the patient and his ability to co-operate, and (3) the intelligence, understanding, and ability of the physician to manage this problem.

The severity of the disease depends on many factors, including the degree of obesity, the age of onset, and the "metabolic behaviour or resistance" of the individual.

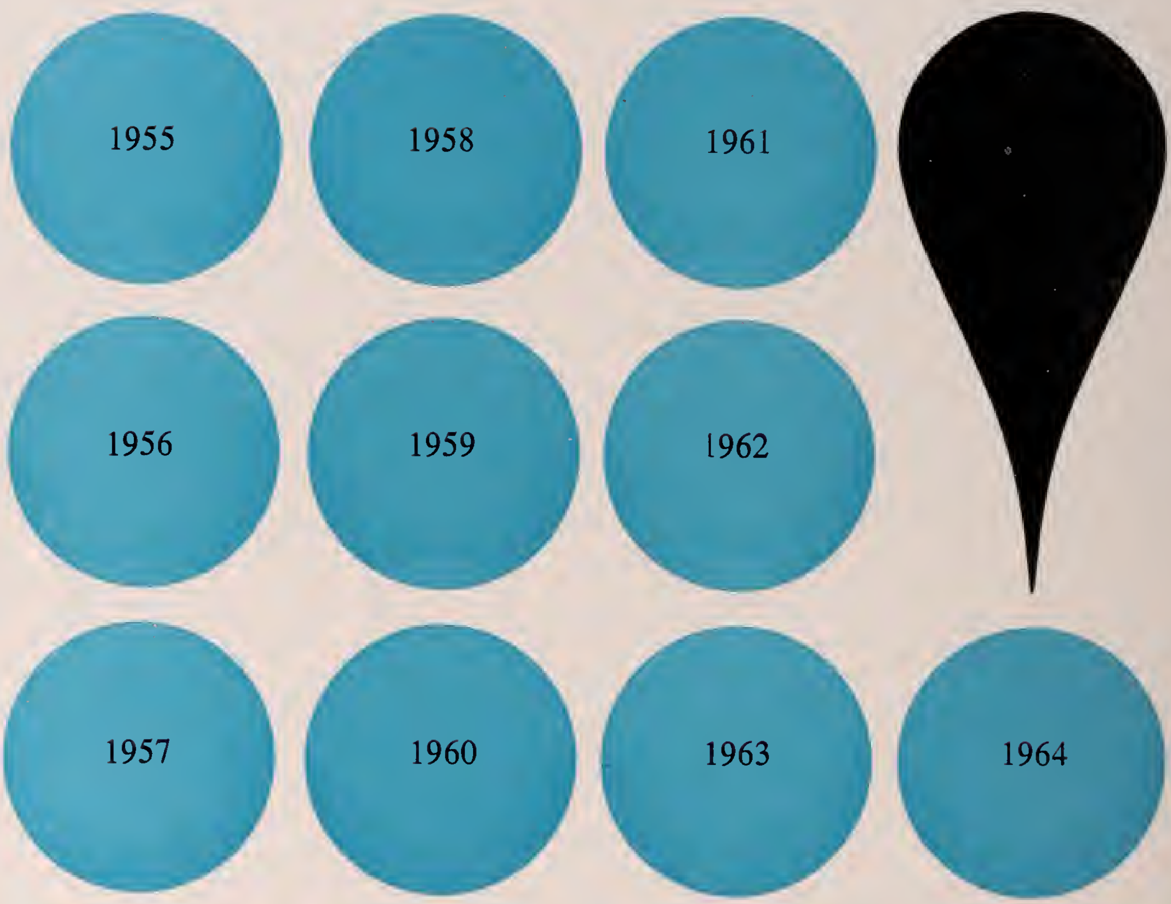
One can predict with reasonable accuracy the success or failure of therapy according to the patient's emotional state, adaptability, marital status, socioeconomic level, environmental stress, motivation, intelligence, education and self-discipline. This last factor is best described by Thomas Henry Huxley, when he speaks of the educated man and how . . . "the most valuable result of education is the ability to make yourself do the thing you have to do, when it ought to be done whether you like it or not; it is the first lesson that ought to be learned and . . . probably is the last lesson learned thoroughly."

The failure rate in therapy is extremely high. Two to five-year cures represent a small minority. Once removed, the obese state demands eternal vigilance to prevent it from recurring. Dieting must become a life-long, almost automatic habit pattern like brushing one's teeth.

Perhaps one should eliminate from therapy those cases which appear predictably hopeless, or at least suggest to these patients that therapy be postponed until such time as success is more likely. One must guard against the strenuous pressure of reduction on those patients in whom damage will be

Continued

The
clear
conclusion
from
10 years'
experience...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done in other areas of their emotional make-up or who will merely be faced with another failure and disappointment in their lives.

Comparable to carcinoma of the lung or carcinoma of the stomach in which the cure rate is low, the cure rate of obesity is also low. However, this does not make it hopeless. Hence the physician must continue to work to improve the results of therapy in this extremely important though somewhat insidious national problem.

David L. Fingerman, M.D.
Minneapolis, Minn.

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1. Gordon, E. S., Goldberg, M. and Chosy, G. J.: A New Concept in the Treatment of Obesity. JAMA 186:50, 1963.

2. Shipman, W. G., Plesset, M. R.: Predicting the Outcome for Obese Dieters. J Amer Diet Ass 42:383, 1963.

The Dilemma of the Fractured Hip

To operate immediately or to delay surgery until a complete medical evaluation may be performed.

Often two doctors approach the hip fracture patient with entirely different points of view as to what is most urgent.

At times the family physician may be diverted from choosing early surgery when confronted by the multiple diseases that often afflict a hip-fracture patient. Thus, a preoperative medical work-up can evolve into a complete medical evaluation and can delay surgery unnecessarily as much as several days.

The hip-fracture patient is usually in his best preoperative condition at the time he reaches the emergency room. From then on, subtle changes can rapidly occur that might mean the difference between life and death. Although there are exceptions to this statement, the general principle is true.

The typical patient who suffers a fracture of the hip usually has one or more other medical problems that have predisposed him to this injury. Usually these patients are aged and quite sedentary. Their bones are osteoporotic and easily fractured. They may in the past, have had one or more cerebrovascular accidents; they may also have had previous myocardial infarcts. The hip fracture may be the result of a newly developed cerebrovascular accident, a myocardial infarct, or some other concurrent illness. Generally these patients are dehydrated and poorly nourished before they reach the hospital, because, in order to avoid aggravating the pain, they decline to take much sustenance. This abstinence further depletes the blood volume and lowers the nutritional level, thus setting the stage for blood clots in the brain, pelvis, or legs. Further, patients will usually not move themselves or allow other people to move them for nursing care. Decubiti and stasis pneumonia rapidly develop under these circumstances.

The patient with a hip fracture, therefore, must be treated as a semi-emergency, and be brought to surgery within twenty-four hours after his admission to the hospital. The only patient for whom this is not true is the one who cannot survive the operation; it should be possible to determine within a few hours after the patient's admission whether he will be able to undergo surgery. It should also be possible within this period of time to take corrective measures, such as digitalizing a patient with cardiac decompensation, im-

Continued

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proving blood sugar levels in the diabetic patient, or giving other emergency medical treatment. It must be kept in mind that the purpose of the medical examination and treatment at this stage is to put the patient in such condition that he can survive the operation. After surgery, more definitive medical treatment may be carried out. If necessary it is possible to undergo a gastrointestinal series two days after a hip-nailing. The patient may be up in a chair the day after surgery. He can be turned on his side or on his abdomen immediately following surgery. His pain can be dramatically relieved so that he may take food and liquids by mouth, thereby greatly decreasing the chances of his developing stasis pneumonia, blood clots in the brain, pelvis or legs, decubiti, or a stress ulcer. During the postoperative period a more complete medical evaluation can be carried out and definitive medical care instituted with relative deliberation during the patient's convalescent period in the hospital.

In summary, the patient who has suffered a hip fracture should be treated as a semi-emergency. Only the treatments necessary to get him into operative condition should be undertaken. In the usual case, twenty-four hours should be enough time to achieve these preoperative goals.

Evan S. Ellison, M.D.
Minneapolis, Minn.

The Editor's Soliloquy

Graduation Day

My son, I wish I had taken the advice of a wiser man than I, when I was your age. Set your pattern early in life, for it will be the one by which you will find yourself living in the very near future. Patterns, good or bad, easily become dominant. I have seen them developing even before the teens, and I have seen the undesirable patterns become almost irrevocable if they have not been firmly eliminated before graduation day. Create a good image; a bad image has a way of surviving despite the fact that it may prove to be false.

Practice the virtues of which there are many: honesty, loyalty, industry, sincerity, humility — you surely know them. It is not necessary to taste all the sins and evils in order to better understand and appreciate the good things in life. Obtain knowledge from which wisdom is derived; it can facilitate and accelerate that acquisition and make it broader, deeper, richer. You, my son, have the basic intelligence to be wise but it will all go for naught unless you fill your brain with information. This can be done only by establishing early the habit of disciplined work and study.

"Be thou familiar but by no means vulgar."* Eliminate the social amenities of the key clubs; do not permit yourself these indulgences until you are old enough to know better. They are too addicting. Drown not your ambitions, your inadequacies, and uncertainties by indulgence in spirits, but solve them through the logical process of your thinking brain. If need be, make a new resolve every day. Eliminate the soporific of excusing your shortcomings by learning to say "I wish I had."

It is sinful to kill, but it is more evil to kill the spirit of your acquaintances with destructive criticism. Avoid this pastime, and if you cannot be constructive in your censoriousness, be silent.

"Give every man thine ear but few thy voice."* Keep an open mind

---

*Shakespeare's Hamlet: Polonius' advice to his son Laertes.

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but have an opinion. Without conviction your mind remains confused and vacillating — without clear focus. You may be wrong but if you are, recognize it rather than defend an error.

"Take each man's censure but reserve thy judgment."* Crusade for the right, but do not pursue it to the point of fanaticism. Respect the law and do not conduct yourself so that you must fear it. It is there for your protection.

Keep your body in physical trim, for it is your most faithful, forgiving, self-sacrificing servant. Do not allow it to become the slave of bad habits. It may eventually fail you if your dissipations are unrelenting.

No matter what your faith, be true to your God, and practice your religion. Only a Divine Being could have devised the multitudinous laws of nature by which we must suffer when we disregard them.

Respect your elders** and keep an ear attuned to your peers. You cannot afford to ignore or flout these readily available founts of precious wisdom and valuable information.

Before time runs out grant that you may attain the wisdom to match the ardor of your youth.

"This above all: to thine own self be true,
And it must follow, as the night the day,
Thou canst not then be false to any man."*

Carl O. Rice, M.D.

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*Shakespeare's Hamlet: Polonius' advice to his son Laertes.
**Fathers' Day June 21.

The Brains of a Pumpkin

"Quackery has the same relation to legitimate medicine that wildcat speculation has to reputable investment banking. Quackery in both medicine and business has many unfortunate victims. A story is told of a famous quack of the eighteenth century. His name was Rock, and he sold a cure-all remedy from an open-air booth near Saint Paul's Cathedral, London. He succeeded famously. One day an old friend of his chanced to pass, and after mutual greetings the two went to a near-by inn to pledge their friendship. The visitor, with the charming frankness of childhood friends, concluded a statement of his surprise at the quack's success in these words: 'Thee knowest thee never had no more brains than a pumpkin.' Instead of becoming indignant, the quack took him to the window and bade him count the passers-by. When twenty had passed, he asked his visitor, 'How many wise men do you suppose were among that twenty?' 'Maybe one,' was the reply. 'Well,' returned the quack, 'all the rest will come to me.' "*

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*Haggard, Howard W., M.D.: "The Lame, the Halt, and the Blind," p. 98.

Error of opinion may be tolerated where reason is left free to combat it.
— Thomas Jefferson

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Unruptured Ectopic Pregnancy

QUESTION: I have a patient 45 years of age who had her last normal period seven weeks ago. Since then she has had periods of bleeding at two-week intervals and vague lower abdominal discomfort with occasional pain in her shoulders for the past six weeks. She was admitted to the hospital because of severe pain in her lower abdomen and left shoulder. She has two children, the youngest ten years of age. She has used a combination of mechanical contraception and rhythm since her last child's birth. Pelvic tenderness precludes definite findings on examination. Would you suggest further measures necessary to clarify the diagnosis?

ANSWER: The combination of lower abdominal pain and pain in the shoulder region suggests free fluid in the peritoneal cavity that is irritating the diaphragm. The pain is probably worse when the patient is recumbent. The association of such pain with abnormal uterine bleeding in a woman of childbearing age should always suggest the diagnosis of ectopic pregnancy. A flat and upright X ray of the abdomen should help to rule out bowel obstruction and pneumoperitoneum. Complete blood studies and sedimentation rate should be routine. A pregnancy test may be most helpful if it is positive. I would then proceed to examination under anesthesia with at least three pints of blood available. If adnexal pathology can be palpated, laparotomy should be performed. If the pregnancy test is negative and the bimanual findings are equivocal, a dilation and curettage should be done. Placental tissue would then explain the abnormal bleeding. The cause of the peritoneal irritation may be determined by colpotomy and direct visualization of the peritoneal fluid and the pelvic viscera. Culdoscopy may give the same information. Culdocentesis with a size 15 needle may obviate the need for either culdoscopy or culdotomy. If the peritoneal fluid is bloody, one may then proceed to laparotomy. However, in the presence of purulent exudate the patient should have adequate trial of antibiotic therapy before surgery is contemplated. I would be interested to hear how your patient was managed. See subsequent observation page 721.

"Beverage alcohol," said a doctor who knew whereof he spoke, "gives you a red nose, a black eye, a white liver, a yellow streak, a green brain, a dark brown breath, and a blue outlook."

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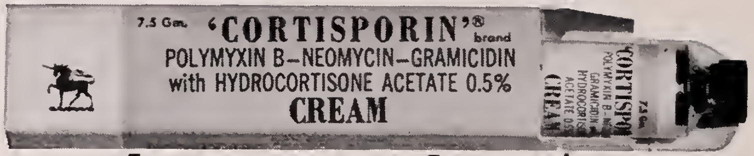
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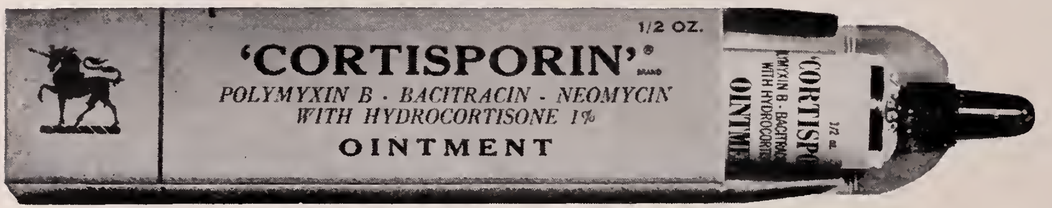
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Fracture–Trauma Conference

Multiple Operated Fractures of the Lower Extremities

Fractures in elderly people have become a more frequent problem because of the greater number of aged persons in our population. The method of dealing with any fracture has to be decided on an individual basis. In this reported case, because of the patient's age and mental state, a prosthesis operation was felt to be the procedure of choice for each hip fracture. In a younger, more active patient internal fixation of the hip fracture would be preferable to the prosthesis.

Case Report

R. S., a seventy-three-year-old lady with signs of early senility, fell at home and injured her right hip. On September 25, 1960, an Austin Moore replacement prosthesis was inserted for treatment of a fractured femoral neck on the right side. She was up in a chair the day after surgery. She was ambulatory in a walker by October 30, 1960.

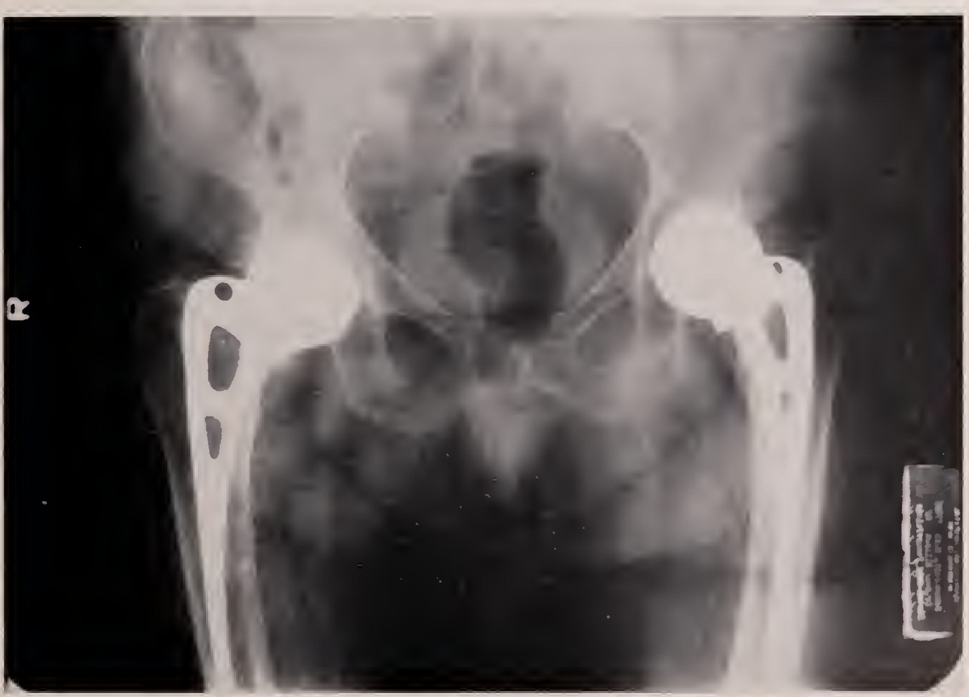

Fig. 1 — Postoperative film October 1960.

On November 17, 1960, she was operated again for a fracture of the femoral neck on the left side. An Austin Moore prosthesis was inserted in this hip also, and she was able to be up in a chair the day after surgery. She began receiving hormonal therapy for osteoporosis at this time.

On June 29, 1961, this patient had an open reduction and internal fixation of a fracture of the distal end of the left femur with an Elliott Plate. At the time of this new injury she also suffered a fracture of the pelvis which was treated symptomatically. She was able to be up in a chair the day after surgery in bilateral padded plaster splints.

By October 6, 1961, she was able to be ambulatory in a walker after three major fractures and operations on her lower extremities.

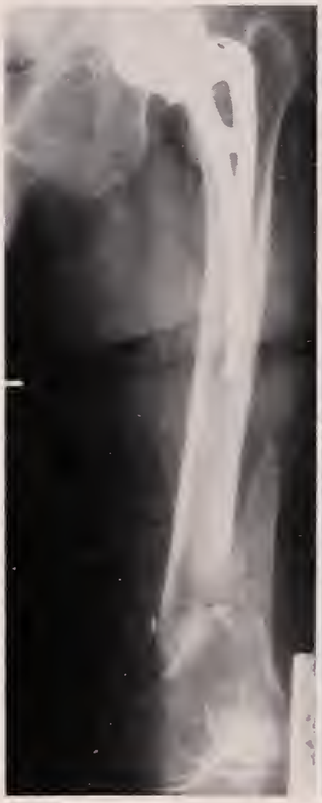

Fig. 2 — Fracture Distal End of left femur, June 1961.

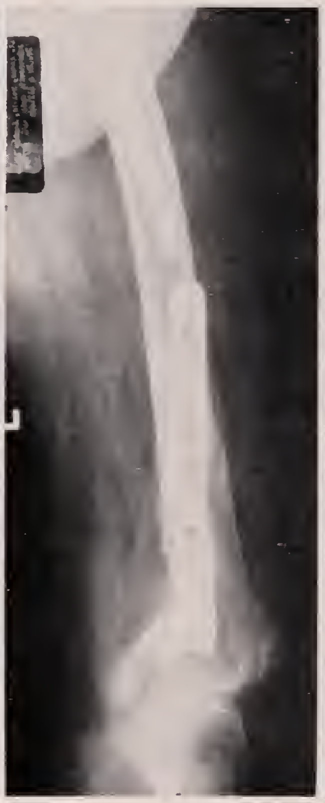

Fig. 3 — Postop film October 1, 1961.

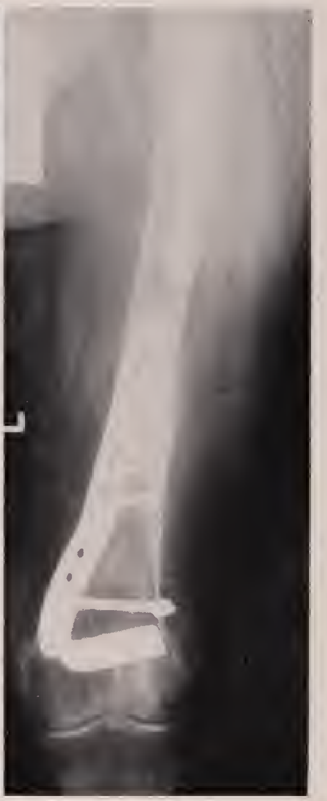

Fig. 4 — Postop film October 1, 1961.

This case illustrates that an elderly semi-invalid patient can survive three major fractures of the lower extremities and still be up in a walker. The method of treatment chosen in each of her fractures allowed her to get out of bed promptly postoperatively. This prevented complications of bed rest such as pneumonia, thrombosis, or decubiti, which are common to her age group.

Evan S. Ellison, M.D.
Minneapolis, Minn.

Fellows who drive with one hand are usually headed for a church aisle. Some will walk down it, some will be carried. — Business Briefs

Tumor Conference

Mediastinal Tumor

A 48-year-old white male was admitted to the hospital for the first time on 10-9-63. Six weeks prior to admission he had noted the onset of persistent substernal discomfort which had led him to obtain a chest film at a mobile X-ray unit. As the reading of this scout film prompted further X-ray studies, he was referred to a private physician for evaluation of a mediastinal mass. Three weeks prior to admission he had noted the onset of severe, sharp pain in the left clavicle and shoulder and subsequently had had to sleep in a semisitting position because of dyspnea and severe pain. A week before admission he noted increasing dyspnea on exertion, a wheeze, and a nonproductive cough.

The patient had not smoked cigarettes for the past 17 years but had been an occasional pipe smoker. There was no history of exposure to tuberculosis or inhalants.

In February, 1963, he had received a routine physical examination for employment and was pronounced in good health. A chest X ray had not been taken at that time; his last X-ray examination taken in California five years previously was reported normal.

Laboratory and Roentgen Examination

Admission laboratory data showed a hemoglobin of 11.5 grams and a white blood count of 10,200 with a normal differential count. Urinalysis was negative. Skin tests for fungi and tuberculosis were also negative.

X-ray Findings

A review of the outside films together with those taken following admission to the hospital revealed (Fig. 1) a large lobulated mass projecting from the left mediastinal border, extending well into the left upper lung field. There was also evidence of a slight widening of the superior mediastinum, suggesting that the mass extended to the right or that lymph node enlargement or vascular engorgement might be present. The tumor seemed to have enlarged somewhat over the period of a month, and there was persistent paralysis of the left hemidiaphragm. It was suggested that

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a lymphoma or cyst of the mediastinum was most likely, but that a large bronchogenic carcinoma could not be excluded.

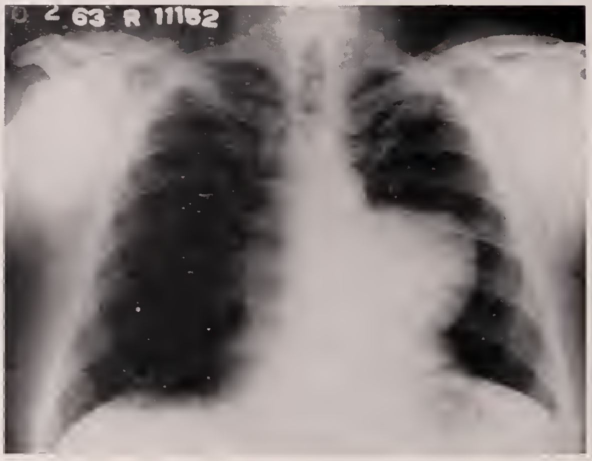

Fig. 1 — The roentgenogram amply demonstrates a large mass extending across the anterior mediastinum and far out to the left. The left diaphragm is elevated and was observed to be paralyzed. There is no evidence of pulmonary collapse or bronchial obstruction.

Bronchoscopy

On 10-10-63 bronchoscopic examination was performed. The trachea was deviated slightly to the right and the right main bronchus was normal. The carina did not appear to be widened. The left upper lobe bronchus was seen to be normal. The left lower lobe bronchus appeared to be somewhat compressed by an extrinsic mass. Bronchial washings from the left upper lobe and left lower lobe bronchi and several deep biopsies taken from the area that showed compression failed to reveal neoplasm or malignant cells.

Scalene Biopsy

On 10-11-63 the scalene fat pads were excised. Microscopic examination showed normal lymph nodes.

Thoracotomy Findings

On 10-15-63 the patient's chest was explored through a standard left thoracotomy incision. Upon entering the chest a remarkably large tumor of the upper anterior mediastinum was visualized, extending far to the left and compressing the left upper lobe. The tumor was broadly adherent to the medial aspect of the left upper lobe, extended superiorly to the innominate vein, inferomedially over the anterosuperior aspect of the pericardium, and on the right to the right extremity of the ascending aorta. Exploration intrapericardially and along the innominate vein revealed no extension. However, because the phrenic nerve was intimately involved and a phrenic paralysis had been noted preoperatively, and also because of the extensive adherence to the left upper lobe, it was felt that grossly the mass represented a malignant tumor. The site of origin was suspected to be thymic. Several mediastinal lymph nodes were excised and sent for frozen section. They did not contain tumor.

The tumor was removed en bloc together with adjacent pericardium, lymph nodes, and the left upper lobe of the lung. Postoperatively the patient has done well.

Pathology

Gross Findings

The specimen was comprised of the left upper lobe and the attached tumor mass, together with superior mediastinal and hilar lymph nodes. The entire specimen weighed 900 grams, the tumor mass representing approximately 700 grams. It was closely adherent to the medial surface of the left upper lobe and in places appeared to be invasive. Medially, the mass was covered by smooth pericardial membrane that showed no evidence of tumor penetration.

Palpation of the tumor revealed softening in some areas, suggesting cystic degeneration. Slices of tumor and lung (Fig. 2) revealed an encapsulated tumor composed of soft, pink-white tissue with numerous areas of recent hemorrhagic degeneration and older cyst-like structures probably representing resolved necrotic processes. There was a suggestion of underlying lobulation.

Where adherent to the lung the capsule was thickened and there appeared to be some fibrosis of the immediately adjacent lung. Otherwise the lung appeared to be normal with no evidence of gross infiltration by tumor.

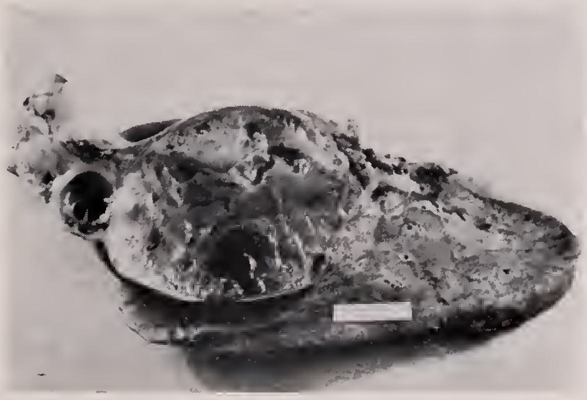

Fig. 2 — The lung has been sliced to show the architecture of the pulmonary and tumor tissue. The cystic and degenerative nature of the tumor is easily seen. Gross invasion of lung parenchyma was not observed.

Microscopic Pathology

Microscopic sections (Fig. 3) showed a highly cellular malignant neoplasm, encapsulated by dense fibrous tissue, with many necrotic areas and considerable variation in morphology at different sites within the specimen. Predominating was an embryonal carcinoma with various degrees of early maturation. Some areas resembled seminoma and others choriocarcinoma. In one area tumor was seen within what appeared to be dilated lymphatics outside the tumor mass, but there was no evidence of direct invasion of

Continued

the lung. All lymph nodes were sectioned and did not show microscopic invasion by tumor. Examination of the surrounding fat did not reveal residual thymic tissue.

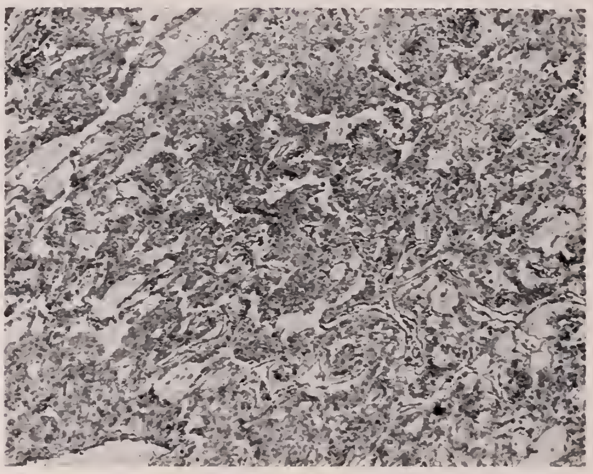

Fig. 3 — The architecture is highly cellular and at this site shows giant cell and syncytial formation suggestive of a chorioepithelioma.

Discussion

The history and symptoms as presented by this patient frequently occur in the presence of an expanding anterior mediastinal mass. Physical examination revealed anterior chest-wall dullness on percussion but little else of diagnostic help. There was no evidence of gynecomastia or testicular atrophy as reported elsewhere in association with endocrine hormone-producing tumors of this type.[1] A 24-hour urine collection was obtained when the microscopic diagnosis became known and was assayed for gonadotropin. The test proved negative, but it is recognized that the specimen may have been obtained too late to prove the existence of elevated hormone levels.

Teratomas

Teratomas of the mediastinum are rare but not unusual tumors, being found in the thorax next in frequency to their location in the gonads of males and females. Benign teratomas are usually unilocular cysts but may occasionally occur in solid form. The latter are more likely to become malignant, the rate varying between 12 and 20% of mediastinal teratomas. When malignant change occurs it usually takes place in epithelial elements of the lesion, thus leading to an adenocarcinoma which in most instances is high-grade. Occasionally the malignant lesion may take the form of a seminoma or embryonal carcinoma similar to tumors seen in the testes. Teratomatous tumors are characteristically located in the anterior mediastinum; only rarely has one been encountered posteriorly. They may assume large proportions and are potentially dangerous lesions which should be removed surgically.

Through the years there has been considerable controversy as to whether or not mediastinal germ-cell tumors originate de novo or represent metastases from testicular teratomas. Willis[2] has reported a small group of cases, collected from the literature, where small relatively well differentiated teratomas of the testes, unsuspected clinically, were found accompanying large rapidly growing undifferentiated, often chorioepithelioma-like, metastasis in the retroperitoneal lymph nodes and mediastinum. In a few such cases the small primary growth had disappeared leaving only a fibrous scar in the testes. Willis felt the only feasible explanation was that the primary focus had originally been actively growing, containing undifferentiated elements that had produced emboli, and that while these later grew actively as metastatic tumors, the tissues of the primary growth in the meantime underwent maturation to a fully differentiated form or suffered total retrogression. It is evidence of this type that has led some observers to believe that even a small scar in one testis invalidates the diagnosis of a primary mediastinal germ cell tumor. On the other hand there is support for a theory that teratomas are a congenital lesion and probably arise as an aberration in local somatic development.

Thymic Origin

Two theories of thymic origin have been advanced for tumor occurrence in the anterior mediastinum. Schlumberger[3] pointed out that the teratoma developed where three germ layers were present in an intimate relation during embryonal genesis, suggesting that mediastinal teratomas arise as defects in bronchial cleft formation, probably in relation to the thymic anlage. Freidman,[4] however, postulated extragonadal germ cells within the thymus as the origin of mediastinal teratomas and stated that seminoma was the earliest and simplest stage of development, the next step being embryonal carcinoma which has biphasic potential and may develop into a teratoma, chorioepithelioma, or both.

Germinal Origin

Recent literature contains several review articles on anterior mediastinal tumors of germinal origin. Kountz et al.[5] surveyed the world literature and found a total of 25 seminoma-like tumors. They added four cases of their own. In only a small number of instances were the testes examined microscopically and, therefore, absolute certainty as to site of origin cannot be assured.

Fine et al.[1] have reviewed extragenital choriocarcinoma in men and have reported 16 cases occurring within the mediastinum — with an additional case of their own. In almost all instances in this series multiple block sections of the testes were obtained and showed no evidence of scarring or residual tumor. Included are tumors containing both embryonal and seminoma-like elements. The paper emphasizes the use of pregnancy tests and the high incidence of gynecomastia. In almost all cases the testicles were atrophic. In Fine's series all cases were autopsied and showed, besides a mediastinal primary, multiple metastases to many organs. In the Kountz series the majority of cases responded well to excision and/or X-ray therapy, and a number of prolonged survivals are cited.

Despite the apparent localization of this lesion it is obviously too early to consider the present case as a possible cure. The literature indicates that the prognosis is generally poor, particularly in tumors of this size, and that aside from the seminoma type, teratomas respond poorly to

Continued

adjunctive therapy. One might speculate that a recurrence of a generally chorioepitheliomatous nature might be responsive to methotrexate.

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Emergency Service

The Minnesota Wing, Civil Air Patrol, has available numerous aircraft stationed throughout the state on a 24-hour basis ready to serve the medical profession. Also, the Civil Air Patrol has state-wide radio communications so that it would be possible to cover the entire State within three or four hours in the event of an emergency.

The equipment and personnel are available to the Association free of charge. Should you need to transport medical supplies to and from outlying parts of the state on an emergency basis or transport patients to the larger metropolitan areas for emergency medical care, the Minnesota Wing is ready to fly. Requests for services may be made by calling 334-2927 during the hours 8:00 a.m. to 4:30 p.m. Mondays through Fridays and LI 5-7628 or JU 8-6548 at other times.

The Wonders of Nature

As a surgeon, I am sometimes called upon to cut away the ureter (the narrow channel that connects the bladder with the kidney) and to implant it into another part of the bladder. When my work has been completed I am ashamed of its crudity. Compared with the job done by a plumber, my joint is a poor and botched concern. Yet when I examine it a year after I am scarcely able to tell which is Nature's joint and which is my own. Some intelligence in the patient's body has made good my failure, paring off redundant tissue here, adding new tissue there, until perfection has been attained. Does that intelligence exist only in the brain? No, for if I divide all the nerves that reach that spot from the brain, the work is performed just as well. If we concede intelligence to the body, we must also concede to it some degree of consciousness. — Kenneth Walker, The Diagnosis of Man

Look wise, say nothing, and grunt. — William Osler

Clinical Path Conference

Proteinuria and Anasarca*

Moderator

The patient, a 40-year-old white male stockclerk, died after an illness of four months. He was married and had four children, the youngest of whom had recently been discovered to have tuberculous lymphadenitis. The patient had first been seen by a staff member six years prior to death, at which time, except for evidence of psoriasis, he had appeared to be free of organic disease. Five years earlier he had had bloody urine following intercourse, which was attributed to a ruptured small urethral vessel.

Previous Illness

In October of the previous year he had had an onset of obscure symptomatology, feeling tired and "sick." A physical examination at that time was essentially negative; but because of a 2+ albumin with some casts in his urine he was admitted to another hospital for study. Laboratory data at that time included urinalyses in which sp. g. varied from 1.027-1.029 and albumin from a trace to 2+ (1.5 gm./liter when quantitated); on two occasions hyaline casts were noted. Hemoglobin varied from 17.6 to 18.7 and was 16.7 gm.% after removal of 500 ml. of blood. White blood count and differential were normal. Platelets numbered 184,000. No LE cells were seen. Sed. rate was 31 mm./hour; cholesterol, 370 mg.%; total serum proteins 6.1 gm.%; albumin, 3.2 gm.%; globulin, 2.9 gm.%; urea nitrogen 13 mg.%; uric acid 7.1 mg.%; urea clearance, normal; PSP excretion 46% in 15 minutes, 78% in one hour; BMR 12%. Throat cultures grew Streptococcus mitis and Aerobacter. Urine culture grew a coagulase negative staphylococcus and Streptococcus fecalis, but no tumor cells were found in the urine. Cystoscopic study was negative. Intravenous pyelogram showed poor visualization of the calyces in the left kidney; but left retrograde pyelography was normal. The electrocardiogram was normal. He was discharged with a diagnosis of gouty nephritis.

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*Presented at Mount Sinai Hospital, Minneapolis, Minnesota, October 13, 1963.

Continued

Readmission

He was then readmitted six weeks later because of a five-day history of epigastric pain. It was then considered necessary to rule out neurosis, gastrointestinal disease, urinary tract lesion, and psychosis. Gallbladder, upper and lower gastrointestinal studies were negative, and laboratory data now revealed that his uric acid was 4.9 mg.%. Physical examination was essentially negative. He weighed 187 lbs. The urinalysis, in which albuminuria was up to 4+, showed some granular casts; blood urea nitrogen 13 mg.%; alkaline phosphatase 11 K.A. units; cholesterol 344 mg.%; amylase 58 Somogyi units; ceph. flocculation negative; thymol turbidity 4 units; hemoglobin 15.7 gm.%; sed. rate 56 mm./hour; white blood count and differential were normal.

It was thought that he might have a biliary dyskinesia or pancreatitis, and a laparotomy was performed. The pathologist's report indicated slight serosal fibrosis. Following the operation ankle edema developed insidiously and then spread up to the waist.

Present Illness

Physical Findings

He was then admitted to Mount Sinai Hospital. Physical examination revealed an obese man, somewhat short of breath, with massive edema extending up to the abdomen anteriorly, and to the second lumbar spine posteriorly. Shifting dullness and a fluid wave were demonstrated in the abdomen. Blood pressure 140/90; weight 221 pounds; height ?. The neck veins were not distended. Subsequent blood pressure was 170/110. Heart tones were normal, with no murmurs. Rate and rhythm were normal. Left base was slightly dull with poorly transmitted spoken voice. A right upper quadrant scar was healing well. The liver and spleen were not felt.

Laboratory Data

Hemoglobin 15.4 gm.%; red blood count 4.87 million; white blood count 5,500; differential normal; sed. rate 6 mm./hour; 4+ albumin in urine with occasional granular casts and white blood cells. Veneral disease research was negative. Blood urea nitrogen 21 mg.%; uric acid 5.8 gm.%; glucose 100 mg.%; CO_2 30 mEq/1; chlorides 100 mEq/1; cholesterol 490 mg.%; serum protein 4.1 gm.%, albumin 1.2 gm.%; globulin 2.9 gm.%; sodium 135 mEq/1; potassium 4.7 mEq/1.

Quantitative urine albumin was 20.9 gm./day and 36 gm./liter. Addis count was 1,700,000 casts, 700,000 red blood count, 4,600,000 white blood count/12 hours; PSP 47% in 15 minutes and 64% in one-half hour.

The bone marrow showed myeloid hyperplasia. Venous pressure was 20 cm. of water in left arm, 17 cm. water in the left femoral vein. X-ray studies indicated fluid at the left base of the chest and a triangular parenchymal density. The renal shadows were noted to be bilaterally enlarged. Abdominal paracentesis yielded 2,200 ml. of turbid fluid with a specific gravity of 1.010, containing 0.1 gm.% protein, 150 red blood count and 52 white blood count/cu. mm. The blood urea nitrogen rose from 42, ten days after admission, to 92 mg.% just before death.

Dr. Aaron Mark:

The constellation of abnormalities consisting of massive proteinuria, hypoproteinemia, edema and hyperlipemia are quite typical for the nephrotic syndrome.

I would like to list some of the causes of this syndrome. One author has compiled about 48 causes, one of which has been ascribed to heavy metals such as mercury and bismuth. Drugs have been implicated, particularly Paradione, Tridione, and recently Perchlorate and Benemid. Another cause is infection, such as subacute bacterial endocarditis, malaria, and lues. The syndrome has also occurred after allergic or hypersensitivity syndromes such as bee sting, poison oak, or serum sickness. Mechanical factors such as pericarditis and renal vein thromboses are occasionally the cause. It has been noted in generalized diseases such as diabetes mellitus, lupus erythematosus, polyarteritis, amyloidosis, sickle cell disease and Schoenlein-Henoch purpura. It is most often related to intrinsic renal disease.

Renal Vein Thrombosis

The first diagnosis I wish to discuss and discard is renal vein thrombosis, a rather rare entity. At times it is primary; often it is related to inferior vena caval obstruction complicating a malignancy. It has been noted to occur terminally in amyloidosis. An acute renal vein thrombosis can give shock, severe loin (not epigastric) pain, and hematuria. People who have the nephrotic syndrome run a less dramatic course. Diagnostically, nephrograms and caval contrast studies might aid in the diagnosis and theoretically, anticoagulants would be of help. However, normal venous pressure in this patient's legs tends to discount the diagnosis.

Diabetes

Two further possibilities are diabetes mellitus and lupus erythematosus. We have in this case but one fasting blood sugar which is 100 mg%. It has been reported that the nephrotic syndrome may be the first manifestation of diabetes, but this is a rare occurrence. Lupus erythematosus is much more common in women. The patient's serology was negative; there is no history of skin rash; the globulin was never elevated.

Intrinsic Renal Disease

The most common cause of the nephrotic syndrome is intrinsic renal disease. A certain portion of cases follow poststreptococcal acute hemorrhagic nephritis, some occur in the course of chronic glomerulonephritis, and others appear without any preceding symptoms. A convenient pathological classification which has gained favor recently is the following:

1. Membranous glomerulonephritis, in which the abnormalities are confined to the capillary basement membrane.
2. Proliferative glomerulonephritis which shows an increased number of endothelial cells. Renal biopsies have demonstrated this picture in association with acute hemorrhagic glomerulonephritis. Some patients on repeat biopsies will show first one and then the other form, suggesting that they are not completely separate entities.
3. Mixed proliferative and membranous glomerulonephritis.

Continued

4. Chronic sclerosing glomerulonephritis.
5. Lipoid nephrosis. This entity shows minimal or no change by light microscopy but changes in the foot processes of the epithelial cells by electron microscopy.

Primary Amyloidosis

The case under discussion has no evidence to suggest an acute hemorrhagic nephritis. There was no preceding respiratory infection, facial edema, hypertension, or hematuria. The addis count showed a normal number of red blood cells. Any of the first four classifications of glomerulonephritis would be exceedingly unlikely without some hematuria; and it would be unusual for a so-called lipoid nephrotic, one with minimal glomerular changes, to die within a four-month interval. I would therefore look elsewhere for a diagnosis. The one I favor is primary amyloidosis. There is certainly no chronic debilitating process that might suggest secondary amyloidosis.

We arrive at this diagnosis partly by exclusion. The enlarged kidneys, fulminating course, lack of hypertension until late in the course of the disease and lack of hematuria are consistent with the diagnosis. Erythrocytosis has also been described. There has been a recent report of a case of the nephrotic syndrome associated with erythrocytosis, which disappeared as the nephrotic syndrome improved. A renal biopsy in that case was not conclusive. Against the diagnosis is the normal liver, spleen, and heart size, and the normal EKG.

Dr. Earl Hill:

I am interested in the elevated phenosulfthalein excretion. There is apparently some hypersecretion in the tubules and it seems to me that I recall hearing of this in subacute nephritis.

Dr. Aaron Mark:

This is true, but I do not think that you can make the diagnosis of nephritis without hematuria. Now I suppose that, statistically, if you have to bet whenever you have an oddball case, you are probably ahead if you bet on an unusual manifestation of an usual disease, rather than take an unusual disease as such. But, I still am unwilling to make a diagnosis of glomerulonephritis in this case without hematuria.

Dr. Leo Weiss:

Dr. Mark's excellent discussion covers the problem well. He should have been a better gambler and played with the odds. At autopsy the gross findings were relatively simple and such as might have been predicted from the clinical story. Anasarca, ascites, and pleural effusions were present. The only organs that appeared significantly abnormal were the kidneys. The left kidney weighed 190 grams and the right 220 grams. The cortex was normally thick. No medullary changes were seen. The remainder of the urinary tract was quite normal. From the clinical viewpoint, there were no gross features for diagnosing the basis of the nephrotic syndrome. Microscopic examination shows this to be a representative example of lipoid nephrosis or, if one prefers to use the morphologically more descriptive name, membranous glomerulonephritis. The architecture and the glomeruli are more or less intact. The glomeruli are slightly large. The tubules are almost normal, although possibly a little bit dilated. Under higher power the basic alterations are apparent. Looking casually at the glomeruli, one might consider them as normal. But, as Dr. E. T. Bell pointed out, these glomeruli are not completely normal. Almost always, they present a thickened basement membrane, visible under the light microscope when one uses a special stain, such as the azo-carmines (Fig. 1). Even with the aid of electron microscopy the argument as to whether or not it is possible to have nephrotic syndrome in the presence of truly normal kidneys still continues.

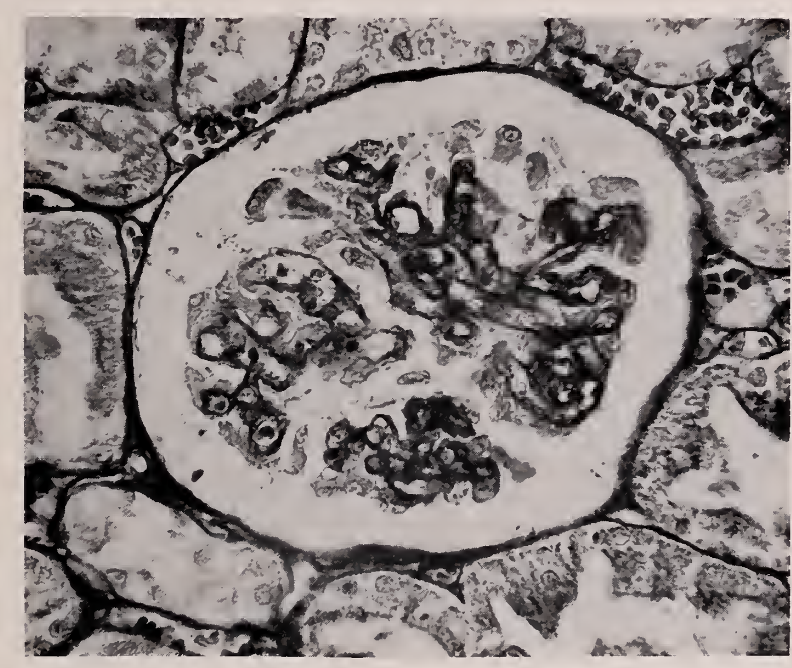

Fig. 1 — Glomerulus (AZAN stain) showing thickened basement membrane.

The other conditions that produce the nephrotic syndrome by means of intrinsic renal disease show similar basement membrane changes, including the lobular type of chronic glomerulonephritis, which may be a more slowly developing form of membranous glomerulonephritis. Transitions between lobular glomerulonephritis and the better known proliferative and hemorrhagic types occur. The Kimmelstiel-Wilson* lesion in both its diffuse and lobular forms, the wise loop lesion of lupus erythematosus and glomerular localization of amyloid deposits all share a common denominator of altered glomerular basement membrane, visible as a thickening by light microscopy.

Clinical Diagnosis:	Nephrotic syndrome.
Dr. Aaron Mark's Diagnosis:	Nephrotic syndrome. Amyloidosis of kidney.

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*See Minn. Med. 46:1097 and 1109, 1963.

Pathological Diagnosis: Lipoid nephrosis
(membranous glomerulonephritis).

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Pliny: Naturalist and Author

Pliny the Elder lived in the first century A.D. He was a constant and avid reader, even refraining from walking because it prevented him from reading. When he had to go from place to place, he rode. While he was eating or being dried after a bath, he had someone read to him in order not to lose time from his books. He is supposed to have read at least 2,000 volumes, compiling his Natural History from the totality of ancient science up to his time.

As a believer in empirical methods and as a keen observer of nature he developed a special interest in the medicinal uses of plant and animal substances. The remedies which he describes are usually fantastic, or even revolting, often referring to the excreta of animals; but for the most part they utilize natural products — leaves and roots, animal parts and organs.

Pliny on Eye Disorders

For defluxion of the eyes, Pliny recommended beef suet boiled in oil to be applied to the affected area. For an eruption about the eye he suggested the ashes of burnt deer horns, and he considered that the tips of the horns were most effectual for the purpose.

"In cases of dry ophthalmia, it is found a very useful plan to take the muscles lying within a loin of pork, and after reducing them to ashes, to pound and apply them to the part affected."*

For diseases of the eyelids the extracted juice of cabbage is used after plucking out the eyelashes separately. The solution is allowed to dry on the lids, and in some instances, when there is rupture of the coats of the eye, woman's milk is added.

She-goats and gazelles are never afflicted with ophthalmia, says Pliny, because they browse upon certain kinds of herbs. Hence it is recommended "at the time of the new moon" to swallow the dung of these animals, coated with wax; and, as goats are able to see at night, it is the general belief that the blood of a he-goat is a cure for those persons afflicted with dimness of sight.

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*Pliny's Natural History, Henry G. Bohn, Publisher, Covent Garden, London, 1856. Translated by John Bostock, M.D., F.R.S. and H. T. Riley, Esq., B.A.

Antibacterial Therapy

II. Newer Agents Having Effects Other Than Anti-Staphylococcal

WILLIAM J. MARTIN, M.D.**
Rochester, Minnesota

AMPICILLIN[1-5] IS a semi-synthetic penicillin which may have potential value because, in addition to being effective against certain gram-positive cocci, it is active against some strains of gram-negative bacilli. It is active against strains of Escherichia coli, Protei, Salmonella, Shigella, and Hemophilus influenzae and parainfluenzae. However, it is relatively inactive against Klebsiella, Aerobacter, and Pseudomonas organisms. The agent has become commercially available as Polycillin.

Organism Affected

Like penicillin G, ampicillin is inactivated by penicillinase and hence has no application in the management of penicillin G-resistant staphylococci. Against susceptible gram-positive cocci, ampicillin, in general, is about half to a quarter as active as penicillin G. However, ampicillin has been said to show greater in vitro activity than the other semi-synthetic penicillins previously discussed against enterococci. Variations in the effect of inoculum size on the minimal inhibiting concentration of the drug appear to depend on the bacterial strain tested.

Route of Administration

After oral administration, serum levels rise and fall rather slowly, with peak levels being reached in about two hours and trace levels being present for at least six hours. Simultaneous administration of probenecid produces higher and more prolonged serum levels of ampicillin. When the drug is given intramuscularly, peak levels in serum are achieved in one hour, and the levels are considerably higher and more prolonged. Ampicillin is not markedly bound to plasma protein. The concentration of the drug in the bile may be three hundred times the amount in the plasma. Only about 25 per cent of the administered dose is recoverable from the urine, and this may reflect its higher biliary excretion rate and enterohepatic circulation with consequent reabsorption from the gastrointestinal tract and destruction therein. During therapy with ampicillin, the serum glutamic oxalacetic transaminase activity may be increased.

Good results have been described in patients having Shigella dysentery; in patients with Salmonella enteritis, results were regarded as comparable to those obtained with previously available agents.[5] Strains of Salmonella resistant to ampicillin have been noted. However, as a generalization, ampicillin shows in-vitro activity against Salmonella organisms which compares favorably with that of choloramphenicol and tetracycline and warrants further in-vivo evaluation.

In the clinical investigation of human adult subjects, 0.5 gm. of ampicillin usually has been given every four to six hours by the oral route. It has been administered intramuscularly in the same dosage. In terms of activity in plasma, an oral dose is equivalent to about half the same dose administered intramuscularly.

Continued

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*See Minn. Med. May Issue, 1964 Page 577.

**Section of Medicine, Mayo Clinic and Mayo Foundation.

Comment

The activity of ampicillin against gram-negative bacilli is relatively narrow when one considers that it is ineffective against Klebsiella, Aerobacter, and Pseudomonas organisms. Since it is also ineffective against penicillin G-resistant staphylococci and is considerably less active than penicillin G against other gram-positive cocci, it may not have as extensive application in polymicrobic infection as has been postulated.

Cephalothin

Cephalothin,[6,7] a cephalosporin C derivative, was discussed previously since its antibacterial spectrum includes staphylococci that are resistant to penicillin G. However, in addition to being active against gram-positive cocci, it is effective against certain gram-negative bacteria including coli-aerogenes, Proteus, and Klebsiella organisms.

Comment

Cephalothin has several theoretic advantages over ampicillin. Its antibacterial spectrum is broader, it is active against penicillin G-resistant staphylococci, and it is not cross-allergenic with the penicillins. It is true that ampicillin can be administered orally and that cephalothin is given intramuscularly, but in a serious infection the latter requirement is not an overwhelming objection.

Colistin Methanesulfonate (Colistimethate) and Colistin Sulfate

Colistin is for all practical purposes a variant of polymyxin B, differing from it in only one of its amino acids and in the configuration of the molecule. Colistimethate (Coly-Mycin) is the form of colistin administered parenterally, while colistin sulfate is given orally for certain gastrointestinal conditions.

Organisms Affected

Like polymyxin B, the newer agent is effective against strains of E. coli, Hemophilus, Aerobacter, Paracolobactrum, Klebsiella, Brucella, Salmonella, and Shigella, but it is employed especially against Pseudomonas organisms. Proteus, Neisseria, and gram-positive organisms generally are resistant to the action of the drug.[8-12] It is less potent than polymyxin B when compared milligram for milligram; and while it has been described as having fewer side effects, this is disputed. Reportedly, when colistimethate is used in doses necessary for control of systemic infections, toxic effects may be expected in 30 to 50 per cent of cases.[10] Impaired renal function increases the likelihood of toxicity. Resistant strains of organisms may be obtained after serial passage in vitro and in animals, and reciprocal cross-resistance with polymyxin B is sufficiently frequent to be considered complete. While colistimethate has been described as being effective in eradicating bacteriuria, it has been much less effective in the treatment of deep-seated systemic infections including abscesses, pulmonary infections, and meningitis — probably, it has been thought, because of the relatively poor blood levels attainable with colistimethate.[10]

Route of Administration

Gastrointestinal absorption is slight; for systemic infections the intramuscular route is employed. Concentrations in the blood after intramuscular administration of colistimethate range from 2 to 10 mcg./ml. with a peak at three to four hours and a duration of eight to twelve hours. However, often the concentration in blood barely exceeds the minimal inhibitory concentration. Levels in urine usually exceed those present in blood by 10 to 20-fold. Studies in children with meningitis indicate that the level in the cerebrospinal fluid is approximately a third that in the blood.

Usually 100 to 150 mg. of colistimethate is given daily in three or four divided doses by the intramuscular route. Some investigators have given 300 to 350 mg. per day. The intravenous route is not recommended. The marketed injectable form contains a local anesthetic and is therefore not suitable for intrathecal administration either. However, the manufacturer has supplied a preparation which does not contain the local anesthetic and which is said to be more acceptable for intravenous and intrathecal use. As noted previously, the oral form, colistin sulfate, is available for certain enteric infections.

Undesirable Reactions

Toxic reactions to colistin include circumoral paresthesia, nausea, rash, pruritus, fever, mild pain on injection, vertigo, ataxia, nystagmus, increased azotemia in patients with impaired renal function, and perhaps transient leukopenia. Blood cell counts should be made periodically, especially during prolonged therapy. Superimposed infection due to resistant strains of micro-organisms has occurred. Disturbances in vision and speech have been reported. Paresthesia of the extremities is less often encountered than that about the mouth. Azotemia usually declines at least within a few weeks after discontinuation of therapy. Colistimethate must be used with particular care in infants and the elderly because of their possibly inadequate renal reserve. Hepatotoxicity of colistimethate recently has been suggested.[13]

Comment

While colistin may have potential value, it has properly been pointed out that it is not a panacea.[10] One should be aware of its relatively narrow antibacterial spectrum, the comparatively poor tissue levels that are attained, and its untoward effects, especially the neurotoxic and nephrotoxic ones. It has not been demonstrated clearly that colistimethate should be favored over polymyxin B in the management of serious infections such as Pseudomonas meningitis. While colistimethate may be less painful than polymyxin B on intramuscular injection, this may reflect its being marketed in combination with a local anesthetic; in the seriously ill patient this characteristic may not represent an advantage of overwhelming proportions. If the production of less pain on intramuscular injection is taken as a paramount advantage of colistimethate, one should recall that employing a 1 to 2 per cent solution of procaine hydrochloride in making dilutions of polymyxin B usually will decrease pain at the site of intramuscular injection.

Gentamicin

Gentamicin (Garymycin) is a new antibiotic which is a mixture of two isomers having similar antibacterial and pharmacologic properties.[14] The antimicrobial spectrum of gentamicin resembles that of neomycin and kanamycin but the newer agent appears to be more effective against strains of Pseudomonas organisms. On in vitro testing, more than three fourths of the Enterobacteriaceae and Pseudomonas organisms studied have been susceptible to 4 mcg. per ml. of gentamicin.[15]

Organisms Affected

Strains of Staph. aureus demonstrate complete cross-resistance to gentamicin and neomycin; gentamicin-resistant staphylococci are also resistant to streptomycin, but streptomycin-resistant strains may remain susceptible to gentamicin.

Gentamicin appears to be quite bactericidal, since usually the minimal bactericidal concentration is the same as the minimal inhibitory concentration or only one to two tubes higher than the latter. In vitro bacterial resistance is said to develop slowly and in a step-wise fashion.[15]

Gentamicin is poorly absorbed from the gastrointestinal tract and for systemic effect is given intramuscularly. Following intramuscular administration of 0.4 mg./kg. every 8 to 12 hours, serum levels are usually 1.6 to 2.0 mcg./ml.; serum levels seldom exceed 4 mcg./ml. Peak levels usually are reached about one hour after intramuscular injection. Binding of gentamicin by serum protein is about 30 per cent. Gentamicin is excreted in the urine in goodly quantities.

Use of gentamicin has been suggested in selected infections of the urinary tract, and the drug may have potential application in other infections. However, the relatively low serum levels attained militate against the likelihood that it will have extensive use as a single agent in systemic infections. In general, the drug should not be given in full dosage for more than seven days. Gentamicin has eliminated Shigella sonnei from the genitourinary and gastrointestinal

Continued

tracts.[16] It has been effective in infections of the urinary tract due to coli-aerogenes, Proteus and Pseudomonas organisms when administered intramuscularly in amounts of 30 mg. two to three times daily.[15] Theoretically, since gentamicin may be more effective than kanamycin against Pseudomonas organisms, use of the newer agent in combination with a tetracycline or chloramphenicol might be preferable to similar use of kanamycin in the empiric management of selected serious infections due to gram-negative bacilli prior to the availability of definitive microbiologic data.

Route of Administration

Oral administration of gentamicin in amounts of 40 to 80 mg. two to four times daily may have application in preoperative preparation of the bowel, in patients having hepatic insufficiency, and in certain infections of the gastrointestinal tract due to such organisms as Salmonella, Shigella, and the coliform group.

Proteinuria, azotemia, cutaneous eruption, and vestibular damage, including that of delayed onset, have followed use of gentamicin. The possibility of inducing vestibular damage is considerably increased in patients who have azotemia.

Comment

Since evaluation of gentamicin is not greatly beyond the stage of preliminary clinical investigation, one cannot currently estimate its future position in the antibacterial armamentarium.

Nalidixic Acid

Nalidixic acid (NegGram),[17] a naphthyridine derivative, has demonstrated activity against certain strains of gram-negative bacilli. The drug recently has become commercially available.

Organisms Affected

In general, it is most likely to demonstrate a bacteriostatic effect against strains of coli-aerogenes, Proteus, and Klebsiella organisms. Conversely, it may be ineffective against Pseudomonas, Brucella, and Shigella organisms, as well as against gram-positive cocci, including staphylococci.

Route of Administration

Nalidixic acid is absorbed from the gastrointestinal tract and is excreted mainly in the urine. The drug is described as being well distributed throughout the tissues of experimental animals, with levels being higher in the bile than in tissue and more closely approximating those in the blood. In human subjects, maximal urinary levels of the drug have been detected in four to eight hours after the administration of a single oral dose of 500 mg., and persistence of the drug in the urine has been noted 12 to 24 hours after its administration.

Preliminary studies have given some indication that an enhanced antibacterial effect may result from conjoint use of nalidixic acid and a sulfonamide.

In the clinical investigation of human subjects, nalidixic acid has been administered in amounts of 2 to 4 gm. daily by the oral route. Via this route it has been investigated mainly as a possible agent in the management of urinary tract infections. More recently a preparation designed for intravenous use has become available for investigational use with the suggestion that it might be useful in certain systemic infections and especially in bacteremia due to Proteus organisms. When administered intravenously, a solution in which 1 ml. contains 100 mg. of the drug is mixed with 250 to 500 ml. of 5 per cent dextrose in distilled water or physiologic saline and given over a period of one and one half to two hours; 0.5 to 1 gm. of the drug has been given every eight hours. However, rapid decreases in the serum levels of the drug after its intravenous administration may necessitate that it be given at more frequent intervals.

Undesirable Reactions

Dermal reactions including pruritus and urticaria, eosinophilia, drowsiness, weakness, headache, stimulation of the central nervous system, and gastrointestinal disturbances including vomiting have followed administration of nalidixic acid. Fever, leukopenia, hepatotoxicity, and an increase in the concentration of serum glutamic oxalacetic transaminase have occurred in subjects receiving the drug, but their connection with nalidixic acid requires clarification. It is advised that the drug not be given in the first trimester of pregnancy and that it be used cautiously in patients who have hepatic or renal impairment.

Comment

As is true of gentamicin, it is not possible at present to evaluate the precise position of nalidixic acid in antibacterial therapy of the future.

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Curbstone Consultations Continued from Page 701

SUBSEQUENT OBSERVATIONS: The laboratory reported that the hemoglobin was 10.0 grams, and the sedimentation rate 40 mm. in one hour. The X rays showed a moderate degree of ileus of the small bowel. The human corionic gonadotropin pregnancy test was positive. On examination under anesthesia a mass was palpated in the left adnexal area adjacent to the left side of the uterus. Pelvic laparotomy showed free blood in the peritoneal cavity, issuing from the fimbrial end of the left tube. The mass was found to be an unruptured pregnancy in the isthmic portion of the left tube. Rather than resect the left cornual area of the uterus, a total abdominal hysterectomy was performed including the tubal pregnancy.

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Grand Rounds

Acute and Chronic Pancreatitis

The pancreas acts primarily as a digestive organ. It secretes a clear colorless alkaline fluid, high in bicarbonate content (up to 150 mEq/liter) which is rich in enzymes. The enzymes secreted consist of two amylases (alpha and beta amylase), a single lipase, trypsin and chymotrypsin (both of which are secreted in an inactive form) as well as a peptidase, collagenase, ribonuclease, desoxyribonuclease I and several proteolytic enzymes.[1]

Pancreatic amylase splits complex starches into simpler carbohydrate blocks. Pancreatic lipase, in the presence of bile acids which also act as an emulsificant, converts neutral triglycerides to mono and diglycerides eventually to glycerol and fatty acids. Trypsin, chymotrypsin and carboxypeptidase reduce proteins to polypeptides and ultimately to amino acids. It should be noted that trypsin is only converted from its inactive form trypsinogen by enterokinase in the duodenum.[2]

The control of secretion is very complex and only partially understood. Pancreatic flow is believed to be regulated by three factors: (1) central autonomic vagal, (2) local neurogenic reflex, and (3) two separate hormonal factors secretin and pancreozymen.[3] Food ingestion constitutes the most effective stimulus. This response appears to depend on the reflex stimulation of the vagus. Shrinkage of glands and the disappearance of intracellular granules is reflected in a flow of enzyme-rich juice. Stimulation of the sympathetic supply results in a diminished blood flow and a reduced enzyme content.

The hormonal influence on the pancreas is profound. Secretin is liberated from the intestinal mucosa to release from the pancreas a voluminous, thin pancreatic juice high in bicarbonate content and low in enzyme concentration. Pancreozymin, also liberated from the intestinal tract, produces a secretion high in enzyme content similar to that produced by vagal stimulation. McCaughn et al.[4] found that pancreatic flow was continuous in

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*Presented as a Medical Grand Rounds at Mt. Sinai Hospital, Minneapolis, March 12, 1963.

Continued

man, but at a low level. Flow was markedly increased by taking food, whether it be rich in protein, fat or carbohydrate.

Hollander and Janowitz[5] state that although the major portion of pancreatic digestive enzymes enter the duodenum in the normal person, a small amount enters the blood stream. Whether or not an "endocrine-exocrine" partition exists, which is altered in certain disease states, or whether a local escape of enzyme into the blood stream accounts for the presence of serum enzymes, is not well understood, Gastrointestinal absorption of pancreatic enzymes does not play a part in serum enzyme elevations.

There are three ways for pancreatic enzymes to enter the circulation: (1) by venous absorption, (2) by lymphatic absorption, and (3) by peritoneal absorption.[6] Dumont et al.[7] demonstrated a direct functional pathway from pancreatic cells to the thoracic duct and then into the systemic circulation.

Clinical Signs of Acute Pancreatitis

Acute pancreatitis may occur in any age group but usually in middle life. The sex ratio appears equal. The onset is usually sudden with severe epigastric pain radiating to the upper quadrants and the back. It may be precipitated by heavy alcohol ingestion or a heavy meal. Marked nausea and vomiting with ileus follow. A shock-like state is noted with hypotension, tachycardia, and cyanosis of the nail beds. The abdomen is tender and distended. Occasionally a pleural effusion is noted. While these are among the findings in the more severe cases of acute pancreatitis, cases of edematous pancreatitis may have rather mild pain and appear not acutely ill.[8] Indeed, this type may pose a diagnostic problem to the clinician and here he must rely on his laboratory aids in the diagnosis.

Pathologic Picture in Acute Pancreatitis

Acute Edematous

The earliest response of the pancreatic tissue in acute pancreatitis is recognized by local pancreatic edema, distention of the lymphatics and vascular engorgement of the pancreas. Drelling[9] believes this to be secondary to local inflammation from the escape of activated enzymes into the interstitial tissues. Apparently the process is initially retarded by enzyme inhibitors within the interstitial fluid in the pancreas. This is reflected in the fact that many cases of pancreatic edema are seen without necrosis.

Acute Hemorrhagic

As the area affected becomes more edematous, the blood vessels become progressively congested until an inflammatory exudate of polymorphonuclear and round cells exude into the lobar connective tissue and into the acini. In most instances, this exudate subsides spontaneously, but may progress to hemorrhagic necrosis, particularly when the swollen pancreas is bound by restrictive capsule. Thus a vicious circle is set up; by increasing pancreatic duct obstruction, lymphatic congestion is enhanced, followed by vascular engorgement and further swelling in a restrictive capsule. Eventually ischemia arises. Pancreatic enzymes may further erode into the tissues and thrombose small arteries and veins. Pancreatic cells appear pale and stain poorly. They are surrounded by areas of necrosis and inflammatory cells.[8,9]

The Ascitic Fluid

An ascitic exudate, characteristic of acute pancreatitis, termed "beef broth," accumulates in the peritoneal cavity, consisting of blood, digested tissues, and pancreatic secretions.[3]

After the acute attack, areas of hemorrhage and liquefaction of dead tissue give rise to small pseudocysts within the tissue.

Etiology of Acute Pancreatitis

Bile Reflux

Opie in 1904[10] postulated that the reflux of bile into the pancreatic ductal system caused the activation of powerful proteolytic enzymes which proceeded to digest the pancreas. Ampullary obstruction, whether by biliary calculus, spasm of the sphincter of Oddi or edema of the duodenal mucosa, could cause a "common channel" to be formed whereby bile could reflux into the pancreatic ducts to initiate pancreatitis. While an effective "common channel" has been estimated to occur in 30-50% of the population, the "common channel" theory of Oddi did not explain those cases of pancreatitis where the bile duct and the pancreatic duct entered the duodenum some distance apart. Others[3,9] question the occurrence of reflux bile flow, noting that the secretory reflux pressures in the pancreatic duct are higher than that of the biliary tract. Clinical evidence of bile in the pancreatic duct in patients with pancreatitis is lacking.

Biliary Tract Disease

There can be no doubt though that there is a high incidence of biliary tract disease in acute pancreatitis. Judd[12] reported that 27% of 1200 patients operated upon for cholecystitis had evidence of associated pancreatitis. Kozell et al.[13] found pancreatitis present in 20% of the cases of choleledocholithiasis (without jaundice) in 1874 autopsies where gallstones were noted.

Common Channel Theory

Rich and Duff[14] further modified the "common channel" theory. They demonstrated experimentally that it was not the bile itself that caused the pancreatitis but rather the pressures under which bile (or other substances) were injected into the pancreatic duct to initiate the process of inflammation. When pressures exceeded 500 mm. H_2O the pancreatic ducts were ruptured and pancreatitis ensued.

They noted pancreatic ductal metaplasia in 13 of 24 cases of acute pancreatitis, and suggested that in those patients with a common channel who develop pancreatitis the pathology was on the basis of pancreatic duct obstruction rather than biliary regurgitation.

Pancreatic Duct Obstruction

The concept of ductal metaplasia has not gained wide acceptance because of the frequency with which it has been observed in normal post-mortem glands and because of its rarity in those patients who died with acute

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pancreatitis. On the other hand, the concept of pancreatic duct obstruction as a mechanical etiology in pancreatitis has been generally acknowledged. Ligation of the ducts of Wirsung and Santorini in dogs, followed by the administration of an agent which increased the secretion flow and rate of the pancreas, produced an acute pancreatitis. Lium and Maddock[15] demonstrated in animals that pancreatic stimulation (where ductal obstruction was present) with secretin, Mecholyl or a heavy meal caused pancreatitis. With rising intraductal pressures caused by mass secretions against an obstruction, in all probability, the pancreatic duct radicals ruptured and released enzymes into the tissues and blood stream.

Other Factors

There is no doubt that other factors are involved in the etiology of acute pancreatitis. Also implicated is an infectious disease, specifically mumps. It is interesting to note that mumps pancreatitis is of the "acute edematous" variety, and never proceeds to acute hemorrhagic pancreatitis.[16] Metabolic causes known are those of essential hyperlipemia, hemachromatosis, kwashiorkor, alcoholism, cirrhosis, hyperparathyroidism, and sprue. Vascular etiology also plays a part in that periarteritis nodosa has been noted in several cases. A toxic factor, methyl alcohol poisoning, is known. Alcohol has been implicated as a precipitating agent in acute pancreatitis.

In summary, although the pathogenic basis common to all factors of acute pancreatitis appears to be pancreatic duct obstruction, secondary factors such as biliary reflux, vascular ischemia, and autoimmune mechanisms play important roles in the different varieties of acute pancreatitis. Dreiling[9] suggests that the acute pancreatic inflammation complicating biliary tract disease is best explained by a reflux of infected bile into the pancreatic duct system, activating pancreatic enzymes.

Laboratory Aids in the Diagnosis of Acute Pancreatitis

It is necessary to distinguish acute pancreatitis from other acute upper abdominal conditions, particularly since patients with acute pancreatitis do not tolerate laparotomy well. The principal conditions which enter into the differential diagnosis are acute cholecystitis, perforated ulcer, upper intestinal (small bowel) obstruction, mesenteric thrombosis and myocardial infarction, all of which require distinctly different management from acute pancreatitis.[17] Here lies the importance of laboratory aids in the correct diagnosis of acute pancreatitis.

Routine blood work will be one of the first steps taken upon admission of a patient with a tentative diagnosis of acute pancreatitis. A moderate leukocytosis and increase in the granulocyte count is common in acute pancreatitis, but is not remarkably characteristic.[18]

Blood Sugar

Hyperglycemia is an uncommon finding when all degrees of pancreatitis are considered, but in severe pancreatic necrosis it is present in most instances. Fasting blood-sugar determinations should be made regularly in every patient suspected of having acute pancreatitis. Diabetes mellitus should be anticipated whenever pancreatic destruction is great.

Serum Electrolytes

Marked disturbances in serum electrolytes are seen in acute pancreatitis, especially depression in blood calcium, potassium and sodium levels. Hypocalcemia has been attributed to the binding of calcium ions to fatty acids in areas of fatty necrosis in and around the pancreas. Tetany has occurred in cases of extensive necrosis. Calcium determinations should be made at regular intervals, particularly between the fourth and tenth day of illness. The changes in blood potassium and sodium are not well understood. Lowered serum potassium values (below 4.0 mEq/1) have been attributed to lowered intake, excessive urinary loss by nasogastric suction and to alterations in adrenal cortical function, and appear to be responsible for, in part, the abnormal EKG changes which are seen in acute pancreatitis.[9]

Serum Amylase

In respect to historical considerations, amylase was first discovered by Magendie in 1846. Schlesinger in 1908 found five to six times as much amylase leaving the pancreas as compared to other organs in the general circulation, and on ligation of the ducts noted an increase in blood amylase. Elman,[19] introducing a new method of measuring serum amylase in 1929, noted a significant rise in the serum amylase in acute pancreatitis.

Amylase normally is present in the blood and is derived from the pancreas, the salivary glands, the liver and other tissues. Normally, a small amount of amylase passes from the acinar cells through the interstitial spaces into the blood stream.[5] Popper and Necheles experimentally traumatized the pancreas, and noted that the amylase content of the veins increased without concomitant changes in the level in the pancreatic arteries and lymph spaces. They postulated that a direct pathway for the passage of amylase to the blood stream existed. This work has been confirmed by Howard, Smith and Reke.[21] Gibbs and Ivy[11] demonstrated that the rapidity with which the serum amylase is detected in the peripheral blood is a function of pancreatic ductal pressure. They demonstrated that if they maintained the ductal pressure at the secreting pressure of the pancreas, a rapid rise in the serum amylase was noted.

Serum amylase is typically elevated from 2-12 hours after the initial onset of the attack, attaining its maximal levels from 12-24 hours later. The serum amylase returns to normal limits in most cases from 3-10 days, depending on the degree of pancreatic damage, the presence or absence of a pancreatic pseudocyst, or recurrent episodes of pancreatitis.

In order to detect transient rises in mild degrees of inflammation and edema, early and frequent amylase determinations are necessary. Early resolution of pancreatitis may be indicated by the rather rapid drop in serum amylase to normal levels. As previously indicated, extensive destruction of the pancreas may cause enzyme production to cease, quickly decreasing the level of serum amylase to normal values. For these reasons it is not possible to correlate the severity of the disease with the degree of elevation of blood amylase. Likewise, a normal enzyme level does not exclude acute pancreatitis.[1]

Differential Diagnosis

Elevation of serum amylase has been reported in a variety of abdominal conditions, making the interpretation of the serum amylase level rather difficult in terms of the pathology present. Some of these conditions are

Continued

known to be associated with acute pancreatitis, and it is important that these nonpancreatic conditions be mentioned.

Biliary Tract Disease

Biliary tract disease has often been associated with pancreatic disease. Meyer et al.[13] found that in a large series 6.9% of patients with cholelithiasis had pancreatic disease, 21.8% with choledocholithiasis had pancreatic disease, and 24% of the patients with choledocholithiasis and jaundice had pancreatic disease. Acute edematous pancreatitis in patients with acute cholecystitis and amylasemia may clear without pathologic change in 24-48 hours by the time of surgery. Roussel reported that the elevation in serum amylase in acute cholecystitis does not seem to bear a direct relationship to the degree of pancreatitis found at the time of surgery and that a high amylase does not contraindicate surgery.[23]

Elevated serum amylase not infrequently follows cholangiography, especially if there is reflux into the pancreatic duct.[6]

Perforated Peptic Ulcer

Perforated peptic ulcers, especially those which rupture posteriorly and penetrate into the pancreas, may raise the serum amylase to significant levels. Rogers[24] observed that 16% of 1000 patients with perforated peptic ulcer had abnormal serum amylase values. Greater elevations were associated with perforations of longer duration.

Small Bowel Obstruction

Small bowel obstruction can give rise to levels of serum amylase corresponding to the most severe pancreatitis. Abruzzio[25] reported four of 20 patients with small bowel obstruction had extremely high levels of serum amylase. The high levels of amylase may be explained through the absorption of amylase fluid passing from the necrotic gut wall into the circulation, or by pressure transmission into the common duct.

Other Conditions

Other miscellaneous conditions responsible for a rise in serum amylase are generalized peritonitis, ectopic pregnancy, infectious hepatitis, uremia (impaired excretion), postgastrectomy, and following the administration of morphine-like narcotics (including demerol) and parasympathometic drugs.

Bogach et al.[26] administered ¼-grain morphine to medical students. They noted that 60% of the medical students given meals after the morphine was administered showed a significant rise in serum amylase. They concluded that patients given morphine, may have rises in the serum lipase and serum amylase suggestive of an acute pancreatitis, (though such pathology be absent).

Domalski and Bryant[27] found elevated amylase values in 24% of 50 alcoholics who did not have symptoms of acute pancreatitis. Dreiling[9] administered alcohol intravenously to the point of intoxication, and noted no increase in the external pancreatic excretion as noted by volume, bicarbonate or amylase. Elevated amylase in alcoholism is thought to be secondary to vomiting, irritation of the duodenal mucosa or sphincter spasm.[6]

Warren[28] observed that 80% of patients with mumps may show increased serum amylase levels. In most cases of mumps, the rise was delayed until the third or fourth day of the disease, persisting 5-7 days. The rise in amylase was directly traced to the infected salivary glands. In this case, the serum lipase proved to be of diagnostic importance in determining whether or not pancreatitis was present.

Urine Amylase

Measurement of urine amylase provides a valuable tool in the diagnosis of those patients with mild pancreatitis and in those patients seen several days after the initial attack when the serum amylase is normal. Urine amylase levels remain abnormal 7-10 days after the serum concentration has returned to normal. Patients with pseudocysts may release amylase into the circulation for weeks after the initial insult.[30]

Normally, the kidney rapidly excretes amylase, clearing it at a rate of 2 ml/min.[31] In acute pancreatitis there is typically a three-fold rise in amylase clearance, which in a period of two weeks, returns to normal.[30] The mechanism for this increased clearance rate is unknown.

Large increments of amylase are required to raise the serum concentration appreciably, and the plasma is an insensitive reflector of the total amount of amylase passing into the circulation before being excreted in the urine. This is why urine amylase excretion is a very sensitive indicator of pancreatic inflammation, days or weeks after the initial episode.

Zieve studied 241 patients with abnormal amylase excretion and found that values in acute pancreatitis frequently, though not invariably, exceeded 100 units per hour. Thirty-four of 35 patient (97%) with amylase excretion exceeding 1000 units/hour had pancreatitis, and 10 of 28 patients with levels below 1000 units/hour (36%) had pancreatitis.

Elevations up to, but not exceeding 1000 units/hour, have been observed in acute cholecystitis and cholelithiasis in Zieve's series. Whether or not a mild pancreatitis was involved, was not certain. (Special note: The only case when the serum amylase may be elevated and the urine amylase excretion low is in the presence of renal insufficiency.)

Serum Lipase

Lipases act on esterase linkages of triglycerides, catalyzing the release of fatty acids and glycerol. Lipase activity is assayed by the estimation of fatty acids liberated in the incubation of the enzyme with triglyceride substrate. Serum lipase elevations tend to parallel those of blood amylase, but generally persist longer (10-14 days) and occur later in the course of acute pancreatitis. Johnson and Bochus reported serum lipase elevations in 81% of 21 patients with acute pancreatitis. Comfort and Osterberg[34] noted elevations of the serum lipase in 31 or 32 patients with acute pancreatitis.

Like the serum amylase test, the serum lipase can be elevated in several other conditions, specifically in patients with hepatobiliary disease, (cirrhosis, infectious hepatitis), intestinal obstruction, and peritonitis. Although Kowlessar[1] reported no significant change in the serum lipase levels following the administration of opiates, Dreiling et al.[9] and Gross et al.[34] have reported significant elevations following the administration of codeine, demerol and secretin.

The serum lipase determination is of considerable significance where

Continued

mumps pancreatitis is concerned. Inflamed salivary glands raise the serum amylase level to extremely high levels in 80-90% of the cases of mumps and thus cannot confirm the diagnosis of pancreatitis. Only lipases rises are significant and diagnostic.

Desoxyribonuclease I (DNA I)

Kowlessar[35] was the first to suggest that the enzyme DNAase I could reflect in the serum pathological changes in the pancreas. The activity of DNAase I appeared to be considerably higher in the pancreas than in other tissues of the body. In 34 patients in whom the serum amylase was 200 units or greater, marked and protracted elevations were noted only in those with acute hemorrhagic pancreatitis. It was concluded by the author that elevations in DNAase I occurred only when pancreatic tissue had been destroyed (as in acute hemorrhagic pancreatitis).

Leucine Aminopeptidase (LAP)

Leucine Aminopeptidase is an enzyme capable of hydrolizing 1-leucyl peptides and is measured by using a chromogenic substrate 1-leucyl Beta Napthylamine HCl (at a pH of 7.1) to determine its activity. (Method of Goldberg and Ruttenberg.)[36] Normal value of LAP is from 64-200 units.

Although initial reports suggested elevation of LAP in acute pancreatitis and in carcinoma of the pancreas, Kowlessar[1] hypothethized that the rise in the serum LAP was related to pathology within the hepatobiliary tree rather than to pancreatic origin. Hoffman et al.[37] observed significant elevations in serum LAP in five of ten jaundiced patients with acute pancreatitis. Although the test may have some value in indicating disease of the hepatobiliary tract and pancreatic complex, Bressler concludes it is not likely to become a useful test in the diagnosis of acute pancreatitis, after investigating 121 patients with various disorders of the hepatobiliary system and pancreas. The serum LAP activity in four of six patients with acute pancreatitis was elevated, but the total serum for the group was considerably below the mean level of acute cholecystitis, cirrhosis, infectious hepatitis, obstructive jaundice, and carcinoma of the pancreas.

Lecithinase A.

Lecithinase A is a pancreatic enzyme that converts lecithin to lysolecithin. Zieve and Vogel[39] initially developed a technique for measuring this enzyme, using a level of 20 units/ml. as the upper limit of normal. As much as a ten-fold elevation of serum lecithinase A was found to occur in acute pancreatitis. Zieve correlated in 15 cases the elevations of lecithinase A with those of serum lipase and amylase and found all three to rise proportionately in acute pancreatitis.

Diagnostic Aids

Peritoneal Aspiration

Peritoneal tap has been stressed as an important aid in diagnosis. When "beef broth" fluid has been removed from the left lower quadrant, there is a strong indication of pancreatitis. High serum amylase levels within the fluid are indicative of acute pancreatitis, but equally high levels have been observed in ascites from bile peritonitis and perforated peptic ulcer.[3]

Roentgenographic Abnormalities

The pancreas, being a soft tissue structure, does not lend itself easily to the conventional methods of study. Some pancreatic lesions can be recognized by virtue of calcification of the gland, as in chronic calcarious pancreatitis or pseudocysts, in which calcium is deposited in the cyst walls. The roentgen manifestations of acute pancreatic inflammation include:

1. Haziness in a scout film of the abdomen.
2. Obliteration of the psoas outline.
3. Elevation of the left diaphragm.
4. Paralytic ileus with its manifestation of the jejunal loop in the left upper quadrant and/or the colon cutoff sign.
5. Basal pneumonitis, pleurisy, pleural effusion in the left chest.

Cholecystography offers little assistance in pancreatic inflammation because of concomitant impairment of gallbladder function.

Chronic Relapsing Pancreatitis

Chronic relapsing pancreatitis is the result of recurrent episodes of acute and subacute attacks of inflammation of the pancreas, leading to varying degrees of destruction and fibrosis. As the process of fibrosis and scarring continues, there is destruction of both acinar and insular tissue with impairment of both exocrine and endocrine secretory function. Chronic relapsing pancreatitis is seen predominantly in males (2.5:1) in their early forties.[3] When destruction of the pancreas has become rather extensive, the classical metabolic defects of the disease appear: (1) calcification of the pancreas, (2) diabetes mellitus, and (3) pancreatic insufficiency, leading to malabsorption and malnutrition (specifically steatorrhea).

Alcoholism and biliary tract disease have an incidence as high as 70% in chronic relapsing pancreatitis.[9]

Nutritional

Nutritional pancreatitis secondary to (1) chronic ulcerative colitis, (2) diffuse jejuno-ileitis, and (3) malabsorption syndrome (Kwashiorkor syndrome) is known. Pancreatic fibrosis is probably on a multiple deficiency basis rather than on a pure protein deficiency.[43]

Metabolic Familial

Two varieties of metabolic familial pancreatitis have been mentioned in the literature. Familial hyperlipemia consists of a triad: (1) hyperlipemia, (2) recurrent abdominal crisis with pancreatitis and pancreatic fibrosis, and (3) premature arteriolar disease.[44] The second variety, as described by Gross,[45] has an aminoaciduria. It is characterized by (1) an early onset in life, (2) predominance in females, (3) lack of gallbladder disease, and (4) calcification of the larger pancreatic ducts. In neither type is the pathogenic mechanism known.

Hyperparathyroidism

Hyperparathyroidism has been implicated as a possible etiological agent. Less than twenty cases of chronic relapsing pancreatitis with this endocrine condition present have been reported in the literature. Wang,[46] in reporting 100 cases of chronic pancreatitis, found no associated hyperparathyroidism noted in any of the cases.

Continued

Symptoms

Abdominal pain is the most outstanding symptom of chronic relapsing pancreatitis. Characteristically epigastric in location, the onset of the pain is gradual with radiation to the back or upper quadrant becoming progressively severe, lasting 24-72 hours. The onset of the pain is often precipitated by a heavy meal or alcoholic intake. Control of the pain through use of opiates often leads to morphine or demerol addiction.

Weight loss is a common complaint and is due to diminished caloric intake and digestive failure secondary to a deficiency of pancreatic enzymes. Likewise, diarrhea is a common symptom, progressing to bulky, foul smelling stools suggestive of steatorrhea in 50% of the patients with chronic pancreatitis.[47] Dreiling[9] noted steatorrhea in only nine (13%) of 71 patients with chronic pancreatitis.

The incidence of jaundice in chronic pancreatitis is about 25%.[48] The jaundice may be due to either associated biliary tree or hepatic pathology.

Physiological Considerations in Chronic Pancreatic Disease

One must recognize the fact that the pancreas has a tremendous functional reserve and that extensive destruction of the gland must take place before pancreatic insufficiency becomes apparent clinically.

Faulty Digestion

With extensive acinar damage, external pancreatic secretion is diminished to the point where faulty digestion and absorption result. Varying amounts of ingested fat and protein are excreted in the stool, giving it the characteristic bulky, fatty appearance. Usually, deficiency states do not reach the stage of clinical recognition in chronic pancreatitis.

Diabetes

Diabetes mellitus forms the second of the three classic symptoms in chronic relapsing pancreatitis. Sprague[50] states that 90% of the islet cell tissue must be destroyed before diabetes becomes apparent clinically. Therefore this complication could only be expected to occur in severe and prolonged pancreatitis. Usually the diabetes is rather mild and the insulin requirement fluctuates with exacerbations and remissions of the disease. Diabetes occurs in 10-20% of patients with chronic pancreatic disease.

Laboratory Aids in the Diagnosis of Chronic Relapsing Pancreatitis

Roentgenographic Studies

Pancreatic calcification is said to occur in 50% of the patients with the disease. Other findings noted may be widening or distention of the duodenal loop due to changes in the head of the pancreas or by pancreatic cysts. On small bowel series, the findings are usually normal in contrast to sprue.[9]

Stool Studies

Alteration in digestive capacity are common in far advanced pancreatitis. Steatorrhea, as evidenced by tannish-white, bulky, foul smelling stools, is primarily due to lipase deficiency. Microscopic examination of the stool with Sudan III stain may reveal excessive numbers of fat droplets, but in general is of limited value. Determination of fecal fat excretion may be indicative of steatorrhea.

Attempts at assessing the stool trypsin content by observing the proteolytic effect of a fecal suspension in a gelatin emulsion (such as X-ray film) have met with little success in this disease.[9]

Digestive Tolerance Tests

Shingleton[51] employed radioactive I-131 labelled albumin and glycerol trioleate in evaluating pancreatic function. Basically, this is a test of the ability of a person to absorb and digest a meal with I-131 labelled fat and albumin. Preceding the test, the thyroid gland must be saturated with potassium iodide for three days beforehand. After the meal is given, blood isotope levels (I-131) are determined at hourly intervals for six hours. Consistently low levels of radioactivity in the blood are diagnostic of steatorrhea. Unfortunately the test as described by Shingleton does not distinguish between pancreatic insufficiency and malabsorption due to other causes. Early and mild cases of pancreatic insufficiency may escape detection. Polacheck[52] modified the forementioned test by administering Viokinase following digestion of the radioactive meal. In seven patients with pancreatic disease, increased plasma levels of I-131 were noted, while seven cases with malabsorption syndrome showed no increase in plasma levels.

Dreiling[9] preferred to use radioactive oleic acid and fat to differentiate between idiopathic steatorrhea and pancreatic disfunction. In his experience, absorption of oleic acid may proceed normally, while triolean absorption is impaired in the presence of pancreatic insufficiency.

Ruffin et al.[53] believe that the determination of blood radioactivity is less satisfactory than fecal stool radioactivity in determining steatorrhea. In 50 patients with high fecal fatty-acid levels, he noted that high fecal radioactive levels indicative of steatorrhea were twice as common as diagnostic levels of blood isotope.

Additional evidence for impairment of fat absorption is supplied by low fasting serum carotine values and failure to respond to a carotine loading test.[51]

Starch Tolerance Test

The rationale for this test is direct and simple. In a normal person amyalytic enzymes will digest a starch meal followed by an elevated blood sugar. With pancreatic insufficiency, a relatively lower blood sugar is noted. In Shay's[54] experience, 50 out of 100 cases with chronic pancreatitis had positive starch tolerance tests.

Pancreatic Secretory Capacity

The secretin test is at present the best method of measuring directly the functional reserve of the pancreas. The duodenum is intubated with a double lumen tube, which effectively separates the pancreatic secretion stimulated by secretin from contamination by hydrochloric acid. Following administration of secretin (1.0 units per kg/body weight) samples are collected for eighty minutes, at which time the response to secretin has been dissipated. The volume, bicarbonate concentration, and the enzyme content

Continued

are measured.[9] Normally secretin evokes a rapid increase in flow of a thin watery pancreatic juice which is high in bicarbonate content and low in enzyme content. The normal values are as follows: Volume flow, greater than 2.0 cc. per kg/body weight; bicarbonate concentration, 90 mEq/liter or greater; and amylase, which may vary from 6-9 units amylase per kg/body weight.[9]

In chronic pancreatic disease, a relative preservation in volume flow is noted with a deficiency in bicarbonate content and enzyme output. The most significant finding is a marked depression of bicarbonate excretion.

Severe cases of chronic pancreatitis may have a decrease in volume indicating ductal obstruction. The same response, however, is noted in those nonjaundiced patients with carcinoma of the pancreas. A screening test for carcinoma of the pancreas has recently been devised whereby the duodenal aspirate has been stained for malignant cells.

Blood Enzyme Studies

Although serum amylase is often employed in the diagnosis of acute pancreatitis, this is not the case in chronic relapsing pancreatitis except in those patients where acute exacerbations are present. It has been suggested that "provocative" enzyme tests may be of value in the diagnosis of chronic relapsing pancreatitis.

Morphine and vagus-stimulating drugs (prostigmine, Methacholine (Mecholyl), and urecholine) supposedly produce an obstructive mechanism at the ampulla of Vater or in the pancreatic ducts. When secretin is administered in conjunction with the forementioned opiates and vagus-stimulating drugs, a rise in serum amylase was noted to occur in a variable number of healthy individuals.[9] The test was based on the observation that pancreatic stimulation without ductal obstruction does not produce a rise in blood enzyme levels.[9] However, when ductal obstruction and pancreatic stimulation are induced together, the blood enzyme (amylase) level rises depending upon the secretory ability of the pancreas. It should be remembered, though, that the degree of obstruction and the amount of pancreatic damage are two variables which must be taken into consideration in evaluating the results.

In a slight modification of the secretin test, Burton[57] made serial determinations of serum amylase and lipase at intervals of 1-6 hours following the administration of secretin and pancreozymin in 213 patients (including normals, pancreatic, biliary and hepatic disease) in a simple evocative test. In a normal pancreas, with submaximal stimulation, a minimal rise in the serum enzymes was noted. When obstruction to outflow of the pancreatic juices was present, a significant rise in serum enzymes was observed. False positive evocative tests were occasionally noted in biliary and hepatic disease (especially cirrhosis of the liver) and in uremia. Burton further established that the elevation of the serum amylase was less likely to occur when an abnormal glucose tolerance curve was present. A direct relationship between impaired glucose tolerance and diminished volume in pancreatic secretion was noted. An inverse relationship existed between the evocative (secretin-pancreozymin) test and glucose tolerance.

Blood Coagulability

Several workers have experimentally created a pancreatic duct obstruction in dogs and have noted a prolongation in the clotting time. Shingleton,[51] using a sensitized clotting test with Paratol C (sodium polyanhydromannuronic acid), demonstrated a measurable increase in the clotting reaction in six of eight patients with chronic pancreatitis, the results of which were confirmed by Moser. It should be noted that an increased bleeding tendency in patients with chronic pancreatitis has not been mentioned in the literature. The reason for the prolonged clotting time is not known.

Robert Schneider, M.D.
Intern
Mt. Sinai Hospital

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10-20. Can be obtainted from Alvin Schultz, M.D., Grand Rounds editor, Mt Sinai Hospital.

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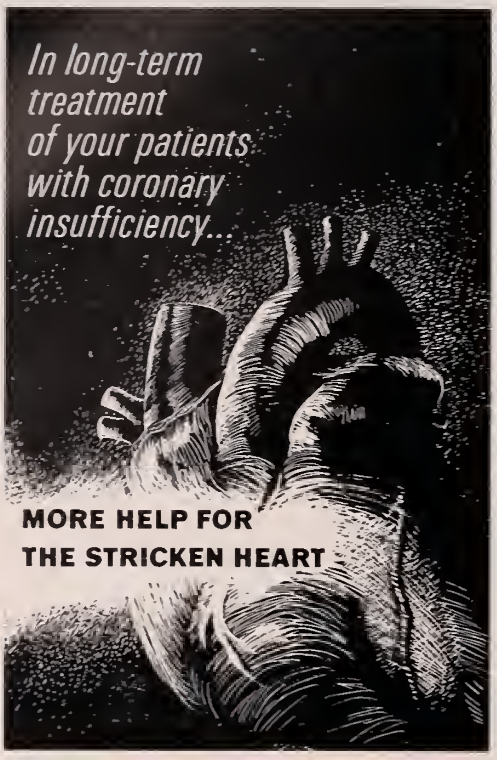
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Abstracts, Briefs and Commentaries

SURGICAL MANAGEMENT OF CHRONIC ULCERATIVE COLITIS

The group surveyed 1230 patients with chronic ulcerative colitis seen between 1954 and 1959. Of this group 205 patients were treated surgically. The authors reviewed these latter cases and emphasized the indications for surgery, the types of operative management, and the results during a postoperative followup of two to eight years.

The average age of the group was 39.9 years. There were 111 men and 94 women in the study. The chronic ulcerative colitis was associated with ileitis and regional enteritis in 48 of the 205 cases. (No cases of primary regional enteritis with secondary involvement of the colon were included in the study.) The average duration of the chronic ulcerative colitis was 8.3 years. Of the 205 patients, 84 had had 154 operations for perineal or abdominal complications of the chronic ulcerative colitis during or prior to the operative period under study. These operations did not include ileostomy, colostomy, or resection of the colon.

The indications for surgical treatment were: (1) complications of the disease, (2) carcinoma, or (3) failure of response to medical management. Complications included fistulae, polyposis, intestinal obstruction, perforation, hemorrhage and infantilism.

Twenty-seven cases of carcinoma were found among the 64 patients explored for this possibility. Forty-one of the 205 patients had had no response to adequate medical management including steroids.

The surgical treatment consisted of total proctocolectomy in 87 patients, usually done in stages. Fifty-seven patients had subtotal colectomies (this term is used to mean removal of more than one half of the colon but less than removed in total proctocolectomy). Thirty-eight patients were treated by partial colectomy (removal up to one half of the colon).

Ninety-four per cent of the patients who had had total proctocolectomy and ileostomy had excellent to good results. However, the other types of surgery resulted in only 74 to 77% good results in the patients traced. Of the 205 cases treated surgically 93% of the 187 survivors were followed for two to eight years. There were 18 hospital deaths, and 43 postoperative complications. Thirty-two individuals died during the followup period; metastatic carcinoma was the etiology in 16 of these patients. Six patients died of late complications directly related to the disease or the surgery. No

Continued

information was available concerning the cause of death in five patients and the mortality was not related to the operation or residual disease in the other five.

Of the eighteen hospital deaths, six followed operations for acute perforations or acute hemorrhage. It was felt by the authors that these complications usually were present when the disease was far advanced and therefore, earlier operation in the course of ulcerative colitis would improve the results by reducing the risk of the operation.

Comment: Very comprehensive article in that it would give guide lines to those individuals who must treat this disease either as surgeon or nonsurgical physician.

Jerome T. Grismer, M.D.
Minneapolis, Minn.

Waugh, J. M., Peck, D. A., Beahrs, O. H., Sauer, W. G.: AMA Arch Surg 88:556, April 1964

PERITONEAL DIALYSIS

This paper presents a clinical experience with peritoneal dialysis in eight cases of acute and four cases of chronic renal failure. In seven of the acute cases the patients survived, but in some of these, hemodialysis also was employed. The relatively simple technique was found to be effective, although slower than hemodialysis. Its main advantages are that it does not require elaborate arrangements, blood, or anticoagulants. The authors conclude that when the peritoneum is intact the method can be employed whenever a temporary kidney substitute is indicated.

Palmer, R., Maybee, T., Henry, E., and Eden J.: Canad Med Ass J 88:920, May 4, 1963.

The purpose of this paper is to report the use of peritoneal dialysis in three patients with chronic uremia and one with glutethimide intoxication. The procedure was technically simple and was carried on in one instance for five days and in another for six days without undue difficulty. The dialysis was initiated by the authors on each occasion but was carried on by graduate nurses under supervision. This procedure is practical and of value in relatively small nonteaching hospitals provided one or more members of the medical staff become familiar with the indications, technical details, and possible complications of the procedure.

Ellis, K., Lea, R., and Drysdale, R.: Canad Med Ass J 88:928, May 4, 1963

A total of 18 peritoneal dialyses were performed in 14 patients over an 11-month period. There were nine patients in uremia, four with non-nephrotoxic intoxication, and one patient in hepatic coma. Chronic uremia may present as a problem of acute renal failure, which may be treated by peritoneal dialysis with resultant significant prolongation of life. A decreased mortality rate might be expected in acute renal failure if dialysis is implemented before the development of the classical picture of uremia. Many non-nephrotoxic intoxicating substances are readily dialyzable. Considerable benefit to the patient and decreased time in hospital may result from the application of this procedure in instances of intoxication with such substances. Peritoneal dialysis may be used in the treatment of intractable congestive heart failure. This procedure may eventually prove to be another means of treating hepatic coma.

Courtesy of References and Reviews
Journal of the American Medical Association

Cohen, H.: Canad Med Ass J 88:932, May 4, 1963

SEGMENTARY VERTEBROTOMY

Vertebrotomy, or the osteotomy of the vertebrae, as a way to correct ankylosis of intervertebral articulations due to spondylarthritis, was suggested in 1932 by V. D. Chaklin. The operational techniques described differ only in minor details. The main indication for the operation has been ankylosis of the intervertebral articulations after spondylarthritis. The present communication is concerned with the segmentary osteotomy of the thoracic vertebrae I resorted to in order to correct kyphosis which had resulted from the congenital concrescence of the vertebrae (a bony union between adjacent vertebrae). In most cases it affects two adjacent vertebrae. Cases in which a greater number of vertebrae are affected are very rare and constitute an extremely grave deformity of the spine.

A case with multiple concrescence in the lower thoracic spine was admitted to my department and showed a rapidly progressing kyphosis with general complaints of a fast growing abnormal curvature of the spine. The girl was well-developed for her age. No abnormalities were found in the chest, abdomen, urogenital system, central or peripheral nervous system. Examination revealed a round kyphosis in the middle and lower thoracic spine. X-ray pictures showed the kyphotic deformity of the middle and lower thoracic spine. The intervertebral spacing was absent over one half to one third of the vertebral body from the 12th to the 8th vertebra. Over the remaining length of the spine the articular spacing was narrowed.

It was decided to perform an operation. The radiographs suggested that if the bony union between the bodies of the concrescent vertebrae were severed at least temporarily, much of the deformity could be eliminated. The plan of the operation was as follows: to obtain access to the bodies of the vertebrae through the pleura; to incise the bony union from the 12th to the 8th thoracic vertebra; to gradually reduce the kyphosis and, thus, minimize the malformation. The kyphosis of the vertebrae could be clearly seen. Instead of normal intervertebral discs between the bodies of the 8th through 12th thoracic vertebrae there were bony unions jutting forward in the shape of fillets. Using elevators and an osteotome, the bony fillets were dissected. Thus, the concrescent part of the spinal column was divided into four segments. The anterior longitudinal ligament was likewise dissected in the transverse direction level with the cuts. When the spinal column was unbent after the osteotomy, the formerly concrescent vertebrae could be seen fanning out, with well-defined slots between them. The patient was put into a plaster bed. No attempt was made to straighten the spine instantaneously. Some complications occurred and were treated. After a month a plaster bodice was applied. On the third day after the application of the plaster bodice the girl was dismissed from the hospital.

After six months the plaster bodice was removed. The curvature of the spine had been practically eliminated. The girl had grown five centimeters. Radiology proved the correction of the kyphosis. According to the date available, the girl's condition thirty-two months after the operation remains good.

Continued

By analogy with the segmentary osteotomy of the extremities this procedure has been termed "segmentary vertebrotomy."

Tsivyan, Ya. L. D.M.,*

*Chief of the Orthopedics and Traumatology Department, Novosibrisk Orthopedics and Traumatology Research Institute Novosti Press Agency (APN)

CLOSED ABDOMINAL INJURY

Intra-abdominal injuries are not always easy to diagnose or exclude, especially in view of the associated lesions often present, such as head injury, alcoholic intoxication, kidney contusion, shock, major orthopedic injuries and so on. In 23 cases treated at Bridge of Earn, 1954 to 1961, the liver and urinary bladder were the organs most commonly damaged. In 12 patients, associated bone injuries were present.

The surgeon's first duty in such cases is to decide whether laparotomy is essential. This is extremely urgent, for in cases of injury to a hollow viscus the mortality rises with each hour that operation is delayed: beyond 24 hours no such patient can be salvaged. Well-founded suspicion calls for laparotomy. "Better to look and see than wait and see" — remembering that modern laparotomy carries only an infinitesimal mortality. Pain, tenderness and guarding, rigidity, peritoneal irritation, absence of bowel sounds, pulse rate and blood pressure must all be properly evaluated. A normal pulse may accompany liver rupture.

Pain in the left shoulder (Kehr's sign) and the phrenic point test of Saegesser were both negative in cases of ruptured spleen. Radiography failed to demonstrate free air in the peritoneum in the three cases of viscus perforation and proved of no value in the diagnosis of rupture of a solid viscus. However, it is of the greatest assistance in the diagnosis of traumatic diaphragmatic hernia.

Courtesy of World-Wide Abstracts

Mathieson, Al: Brit Med J 1962/5307:749

HEREDITY AND PSORIASIS

A kindred of 815 North Carolinians with a high incidence of psoriasis vulgaris is described. "The disease segregated as a simple autosomal dominant trait with a late age of onset and penetrance of about 60%. Males and females were equally affected, serum levels of uric acid and cholesterol were not elevated, and no one possessed the rheumatoid factor." The incidence of arthritis was 2.7% in the kindred (8.1% among the psoriatics), but neither frequency is thought to be statistically significantly increased above normal. It is suggested that conflicting reports about the inheritance of psoriasis are due largely to differing methods of study and, perhaps, to a failure to differentiate severe forms of psoriasis from other disorders. It is pointed out that more than one mutant allele may occupy the "psoriasis locus" and that mutation at a locus other than the one studied by the authors may also produce psoriasis.

Courtesy of References and Reviews
Journal of the American Medical Association

Abele, D., Dobson, R., and Graham, J.
Arch Derm 88:38, July 1963

PRIMARY LUNG ABSCESS

Primary lung abscesses were reviewed over a fifteen-year period. Sixty-six patients with definite air fluid levels were diagnosed as having abscesses, and these diagnoses, correlated by history and physical findings, were followed as to their eventual outcome. The pathogenesis of the abscess could be definitely established in only 24 of the patients. Bacteriologic studies usually revealed a mixed flora. All patients were initially treated with antibiotics and nonoperative therapy. Failure of the abscess to respond promptly to this treatment was considered an indication for surgical therapy. Forty of the 66 patients required some type of operative treatment. This included pneumonectomy in three patients, lobectomy in nineteen, segmental resection in ten, and drainage in eight. No deaths occurred. Morbidity, however, was relatively high. A bronchopleural fistula developed postoperatively in 13 patients and empyema occurred in three. Two of the remaining 26 patients who were treated medically subsequently died despite medical therapy.

The presenting symptoms were usually obscure and consisted primarily of productive cough with sputum, pleurisy, chills, and fever, and interestingly enough, hemoptysis in 45% of the cases. All lobes of the lung were involved except for the middle. The two deaths that occured both resulted from hemorrhage as a result of erosion of the abscess into the major pulmonary arterial branch.

Comment: The authors pointed out a very significant finding. In the cases studied the treating physician had made no further attempt toward adequate bacterial identification. The authors felt that the presence of multiple types of antibiotics had "evoked a less aggressive attitude in the physicians towards adequate bacterial identification" than would have been evident in the preantibiotic era. Although a great many types of pulmonary abscesses can be treated successfully by medical therapy, this is still a disabling disease with resultant decrease in lung function, prolonged economic loss, or hospitalization. High morbidity after surgical resection (40% of the cases) indicates that this still presents a formidable challenge to both the surgical and the nonsurgical clinician.

Jerome T. Grismer, M.D.
Minneapolis, Minn.

Collins, H. A., Guest, J. L., Daniel, R. A., Jr.: J Thorac Cardiov Surg 47:383, March 1964

PROGNOSIS IN BREAST CARCINOMA

A personal series of 566 radical mastectomies was studied. The preoperative extent of disease was classified according to the Columbia Clinical Classification (Haagensen and Cooley). In this series of cases, mammary carcinoma in premenopausal women, particularly those younger than 35 years, carried a poorer prognosis than carcinoma in postmenopausal women. In women under 35 the clinical extent of disease may be deceptively favorable. In these younger women, despite clinically early disease, the axilla may be extensively permeated by carcinoma, and the five-year survival rate is surprisingly poor.

Courtesy of References and Reviews
Journal of the American Medical Association

Kleinfeld, G., Haagensen, C., and Cooley, E.: Ann Surg 157:600, April 1963

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Book Reviews

Books are the legacies that genius leave to mankind, to be delivered down from generation to generation, as presents to those that are yet unborn. — Addison

PRINCIPLES OF PUBLIC HEALTH ADMINISTRATION — **John J. Hanlon, M.S., M.D., M.P.H., Fourth edition 1964, C. V. Mosby Company, 719 pages, $11.50.**

The book is a revision of one published just twelve years ago.

In the first six chapters the author presents the history and development of public health and gives a broad outline of the health problems associated with the present fast moving world.

The next six chapters are devoted to public health organization and administration, including many phases of modern management.

Part three (19 chapters) covers, in considerable detail, specific health problems and programs that have been developed and expanded to cope with the situations of today.

The book contains a wealth of valuable information on public health, preventive medicine and related disciplines. It should be a good reference for the medical practitioner as well as being useful to all those engaged in this field.

Embracing such a variety of detailed information, the text is often heavy reading.

G. F. Amyot, M.D.
School of Public Health
University of Minnesota

ANESTHESIA FOR INFANTS AND CHILDREN **— Robert M. Smith, M.D., 2nd Edition, C. V. Mosby Co., St. Louis, Missouri, 1963. Cloth bound $12.00.**

The author is eminently well qualified to write with authority on this subject. He also has the good judgement to sense that, in the four-year interval since the first edition appeared, changing concepts have evolved in pediatric anesthesia, and their integration with the basic text is well done.

This is a complete text in the sense that all phases of the subject are discussed. Dr. Smith assumes that those who will seek out this book will be familiar with the essentials of general anesthesia. Accordingly, he omits detailed description of basic information concerning agents and techniques which are available in most anesthesia texts. He places greater emphasis on information which some anesthesiologists may lack when called upon to care for infants and children.

Dr. Smith presents the subject in 31 chapters divided into four major categories: (1) Basic biologic and physiologic behavior of infants and children, (2) Agents, techniques and equipment, (3) Management of anesthesia for specific surgical procedures, (4) Special problems in the care of infants and children. Included in the latter group is an interesting chapter on the legal aspects of pediatric anesthesia.

Throughout the text, the author presents revisions of the original volume whenever current concept changes arise. He discusses the sudden rise in acceptance of halothane and the uncertainty pursuant to reports of possible liver toxicity. He notes the abandonment of ether and divinyl ether in many institutions, the effectiveness of external cardiac massage, concepts concerning profound hypothermia and hyperbaric oxygen.

The expressed intent of the author is to present a comprehensive text on pediatric anesthesia by organizing and evaluating pertinent information and discussing this material in the light of his own experience. There is a consistency of delivery which denotes, without question, that the author is forwarding his views. The product of his efforts is a well written, knowledgable, authoritative volume which deserves the attention of all anesthesiologists, pediatricians and pediatric surgeons.

D. S. P. Weatherhead, M.D.
Minneapolis, Minn.

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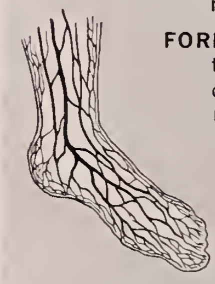

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Special Article

Emergency Red

A Plan for Hospital Personnel in the Treatment of Cardiac and Respiratory Emergencies

IRVING GREENFIELD, M.D.
Minneapolis, Minn.

"EMERGENCY RED" is an audible signal word indicating to all professional hospital personnel that an extreme emergency has occurred somewhere in the hospital. Experience has demonstrated that education, training and discipline of personnel, in the anticipation of an emergency, has often resulted in prompt, orderly and intelligent action when a disaster or emergency occurs. Consequent upon this there is often a real increase in the saving of lives.

Our records indicate that cardiac and respiratory emergencies occur more often on the surgical and medical wards of the hospital than in the operating room. For many years the personnel in the operating room have been trained in anticipation of this disaster, and because of this specialized training they have been frequently called upon to help in this emergency when it has occurred. Due to the co-ordinated and well directed efforts of this highly specialized group several lives have been saved.

In 1952 the Medical Staff of Mount Sinai Hospital directed that the entire house staff and nursing category be instructed in the most recent methods of cardiac and respiratory resuscitation. The Medical Staff also established a permanent cardiac and respiratory resuscitation committee.[1-3] It was the duty and responsibility of this committee to evaluate and make recommendations as to what method, equipment and procedures should be used in this emergency.

Each year a series of lectures and demonstrations are given to all of the professional personnel of the hospital and to many in the paramedical fields. Frequent exercises using numerous teaching aids and mannequins are

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*Director of Department of Anesthesiology, Mount Sinai Hospital.

Continued

held about four times a year with the entire nursing category and house staff. By this method we are able to teach and demonstrate the latest methods of mouth-to-mouth breathing and external cardiac massage. Thus an opportunity is presented for the experienced nurse to practice under supervision and for the novice to be indoctrinated in the plan. The co-operation, willingness and enthusiasm of the entire nursing personnel to participate has been the most important factor in its high degree of success.

It is necessary that all become familiar with the problem. Why it is essential to have everyone understand this situation can be best illustrated by our experience with the problem of communication. It was stressed that all telephone messages involving the telephone operator be curtailed until the emergency is over, for it was important that the telephone operator proceed with her assigned duties in the shortest period of time. It was surprising to learn that once the importance of the telephone operator and her duties was explained to the entire hospital personnel, the number of telephone messages and calls practically disappeared during the time of the emergency.

Discussions and consultations are held frequently with the Engineering and Maintenance Department. The Engineering Department has designed a compact mobile cart that carries all the necessary equipment and drugs. A continuous and deliberate effort is made by Central Supply to keep this unit efficient, so that when anything is needed it is readily available.

The Necessary Supplies

Drugs

Drugs have been kept to an essential minimum. In this manner one is not confronted with a multitude of drugs to cause confusion. The following have proven useful:

1. Adrenalin
2. Isuprel (Hydrochloride — Isoproterenol hydrochloride)
3. Aramin (Bitartrate — Mataraminol bitartrate)
4. Pronystol (Hydrochloride — Procainamide hydrochloride)
5. Cedilanid
6. Vasoxyl (Hydochloride — Methoxamine hydrochloride)
7. Calcium Gluconate
8. Sodium Bicarbonate
9. 1-Molar-lactate

Equipment

The cart is equipped with a small but efficient spotlight. An electrical outlet plug box is provided so that all of the various pieces of electrical equipment can be plugged into the plug box, thus avoiding the use of long extension cords going to the electrical outlets in the room. The cart is so constructed that it is divided into two sections that fold together and can be tightly closed, thus giving it greater mobility. It is painted white with a single red line about three inches wide encircling the entire unit. It is inconspicuous to the visitors that may see it being wheeled down the corridor, but it will be recognized by all hospital personnel. It is also provided with an emergency elevator key so that the elevator can be controlled manually and not automatically.

1. A complete endotracheal outfit, including a laryngoscope and a set of blades for infants, children and adults, and a number of various sized endotracheal tubes and adapters and a breathing bag are included.
2. Two E Oxygen tanks with a regulator and flow meters so arranged and set that a simple twist of the valve is all that is required to get the oxygen flowing.
3. A portable suction machine with a long set of plastic tubes.
4. A set of good suction catheters.
5. A container of sterile syringes and needles of various sizes.
6. A complete cutdown tray with the necessary intravenous fluids.
7. A defibrillator embodying the essential features for internal and external defibrillation. This should also include an oscilloscope and an external pacemaker.

Recently the routine hospital bed board has been replaced by a painter's scaffolding plank. The average hospital bed mattress is too soft and resilient to carry out external cardiac massage. By placing the patient on this long scaffolding and bracing it at both ends of the bed, a very firm surface is thus provided and a much more effective external cardiac massage can be carried out.

Operation

Emergency Red

When an emergency occurs anywhere in the hospital and those present cannot handle the situation the telephone operator is asked to put in "An Emergency Red." Those responsible for resuscitation then converge to the designated station. The person who placed the "Emergency Red" signal with the telephone operator returns immediately to the patient and institutes mouth-to-mouth breathing and external cardiac compression. The telephone operator places the "Emergency Red" signal on the visual system and makes three appropriate announcements over the public address system. Should any house officer be within range of either the visual or public address system he must immediately respond and go to the station. The telephone operator then contacts Central Supply so that the necessary equipment may be brought up to the patient's room.

The Response

It has been observed that at the time of day when the hospital is at its peak of activity, that is from 7 A.M. to 11 P.M., it requires about forty-five seconds before an intern or resident, or an additional nurse enters the patient's room. It also takes about forty-five seconds for the equipment to arrive from Central Supply. Upon one occasion an "Emergency Red" was answered within eighteen seconds. It is gratifying to note that as each person comes into the room he assumes his rehearsed and responsible duties, and the procedure develops without confusion, running around, or the shouting of orders for medications, defibrillators, oxygen, endotracheal tubes, suction machines, etc.

The Resuscitation

External cardiac massage and mouth-to-mouth resuscitation are continued by those present until additional help arrives. As soon as possible the patient is intubated with an endotracheal tube and respiratory resuscitation is carried out using 100% oxygen and a breathing bag. The patient is placed on the rigid bed frame in order to insure a more effectual chest compression. A cutdown is done and used for any indicated drug therapy. A portable electrocardiogram (or oscilloscope) machine is brought in and connected to the patient to see if he is in standstill or ventricular fibrillation. If he is in standstill, external cardiac massage is continued; if he is in ventricular fibrillation, attempts at external defibrillation are made, using the external defibrillator. If this is successful, external cardiac massage is continued in an effort to see if the heart can be restarted. These efforts are continued until the attending physician arrives or until a responsible intern or resident gives the necessary orders to discontinue all efforts in case the patient shows no signs of reviving.

The Benefits

That the efforts of the organized resuscitative group is worthwhile may be judged from the fact that over a ten-year period three hundred and sixty "Emergency Red" calls were answered. We were able to resuscitate ten patients, who were able to leave the hospital and assume a level of activity that corresponded to that which they had participated in prior to their hospital admission.

Summary

"Emergency Red" is an emergency hospital signal that sets in motion an organized group who have been trained in the extreme emergency of cardiac and respiratory resuscitation.

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3. Kouwenhoven, W. B., Jude, James R., Knickerbocker, G. Guy: Amer Med Ass July 9, 1960, Vol. 173:1064.

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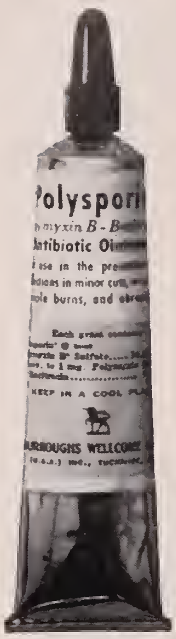

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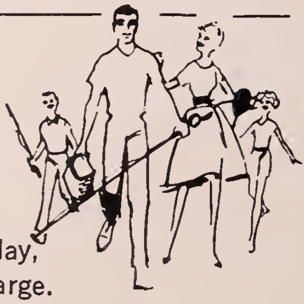

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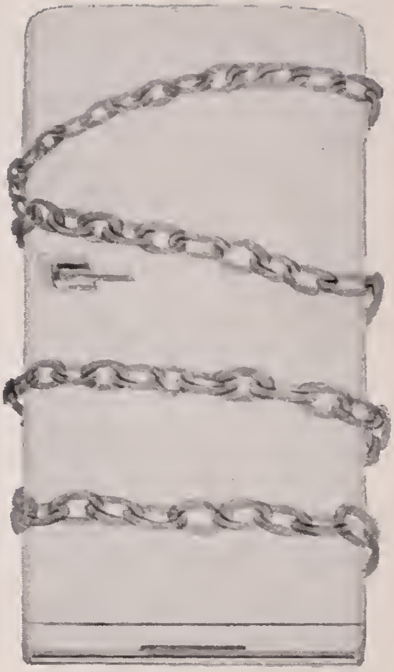

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President's Letter

Business sessions of the Minnesota State Medical Association are usually conducted with such courtesy and decorum that it might be difficult for the casual onlooker to realize the vital importance to everybody concerned of what goes on.

The recent sessions in Rochester constitute a case in point. Business on the floor of the House moved smoothly under the efficient guidance of the Speaker of the House, Dr. John L. Falls of Red Wing. But recommendations were quietly endorsed which had been warmly debated in reference committees and which showed clearly that medicine in Minnesota is really coming to grips with the social problems of our times.

I want to call your attention, especially, to four of these actions, in case anybody who was present should have missed their significance. I also want to note, by way of introduction, that the fine reference committees which served the 1964 session were fully aware of their importance, as also were the officials and members who took the trouble to appear before the reference committees to thrash out their varying points of view. The value of the reference committee system for handling Association business was never more apparent than it was at the Rochester meeting.

The first action I want to mention was the rejection of a resolution from one specialty group which demanded higher fees for services to Kerr-Mills beneficiaries. This resolution was rejected in favor of the creation of a special committee on fees to be headed by Dr. Falls who did so much, himself, to secure passage of the Kerr-Mills law in Minnesota. The committee is to explore the whole question of fees for welfare and Kerr-Mills beneficiaries. Especially, it will consider the question of whether or not the need for an increase is critical enough to request an additional appropriation from the legislature at the 1965 session. In that case, the committee will have the responsibility for presenting the matter to the legislature. It will also be the first committee on fees ever created by the State Association, and the only official agency for transmitting requests for adjustments in fees to any of the state agencies concerned with medical care. The practice of sending copies of the initial request to every interested state official even before the request has Association backing was particularly deplored.

Two truths emerged impressively from the proceedings. One was that the doctors of the state are bound in honor to fulfill their solemn promises with respect to the care of Kerr-Mills patients until such time as the legislature does take further action. The other was that nothing at all can be done without a change in the law. A second House action deserves special comment here. It provides for another committee study, — this one directed toward our entire experience with Blue Shield. Results of this study could, in my opinion, effect the whole trend of prepayment medical care plans in Minnesota. We badly need to re-examine our philosophy and our purposes with respect to these plans, and particularly with respect to recent developments in Blue Shield. We need to know

Continued to Page 891

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Indomethacin:

A New Antirheumatic Agent*

PAUL J. BILKA, M.D.**
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Minneapolis, Minnesota

INDOMETHACIN** IS a new anti-inflammatory drug that has been undergoing clinical trial in various rheumatic disorders for the past two years. It is a tryptophane derivative: neither a steroid nor a pyrazole compound. Animal experiments, utilizing the techniques of inhibition of edema and granuloma formation in which irritating substances are injected or implanted in rats, demonstrate an anti-inflammatory potency of indomethacin on a milligram of drug per kilogram of weight basis that is ten to 85 times that of phenylbutazone and 4.1 times that of hydrocortisone.[1] Its mode of action is not certain, but the adrenal glands are not necessary for activity of the compound. Of possible theoretical interest is a recent paper by Spiera pointing out certain abnormalities in tryptophane metabolism in patients with rheumatoid arthritis.[2]

Reports from several rheumatic disease centers indicate significant benefit from indomethacin in diverse types of arthritis.[3-7] In rheumatoid arthritis, over 50 percent of patients showed clinical improvement of an objective as well as subjective nature.[3,6] Hart states . . . "in indomethacin we had the first noncorticosteroid agent which produced a predictable and measurable reduction in joint swelling in most cases of active rheumatoid arthritis." In gout, dramatic subsidence of the acute inflammatory reaction, in addition to subjective relief, is reported.[3,6] A high percentage of improvement is reported in patients with rheumatoid spondylitis, osteoarthritis, and "bursitis." Norcross stated: "Indomethacin was more effective and associated with fewer side effects and no evidence of toxicity as compared with phenylbutazone or adrenal steroids in the long-term management of rheumatoid or osteoarthritic patients. It is equally or more effective than phenylbutazone in the therapy of acute conditions, i.e., gout, tendinitis, etc., and also in rheumatoid spondylitis."[5]

Unfortunately, a significant incidence of adverse reactions to indomethacin is also reported, running as high as 62 percent when a dosage of 200 mg. per day was given.[8] The predominant side effects were headache, nau-

---

**From the Department of Medicine, University of Minnesota, Minneapolis, Minnesota.

*Supplied by Merck, Sharp and Dohme Research Laboratories, West Point, Pennsylvania.

sea, and vertigo. Reduction of dosage usually controlled these reactions, but often a significant loss of the antirheumatic effect also occurred. In these reported studies indomethacin was administered in the form of tablets. Investigations of the absorption of indomethacin tablets indicated considerable variation in blood levels, presumed to be due to variability in tablet breakdown. The drug was then given as a finely ground powder in capsule form, resulting in more even and predictable blood levels in both human and animal subjects.[9] It was also observed that lower dosages of the drug were then capable of exerting a specific anti-inflammatory effect and that the incidence and severity of adverse reactions was reduced.[9] This report presents our preliminary experience in a group of rheumatoid arthritis patients who were given the new form of micropulverized indomethacin.

Material and Methods

Fifty-four patients with rheumatoid arthritis and seven with rheumatoid spondylitis or rheumatoid spondylitis with peripheral joint involvement, were given indomethacin in a dose of 75 to 200 mg. per day, the average daily dose being in the range of 100 to 125 mg. per day. All patients had active disease as measured by objective criteria of joint synovial swelling and tenderness and elevated sedimentation rates. On the whole these were patients who were not responding adequately to the more standard forms of therapy.

Medication

The patients took their medication in capsules of 25 or 50 mg. each, usually at meal time, in three divided doses, and occasionally took a fourth dose at bed time. Duration of treatment was from one to 42 weeks with an average of 16 to 20 weeks. Initially all patients were examined weekly, and later at two to four-week intervals. Routine laboratory studies were done on these visits and more extensive studies at bimonthly intervals. Placebo substitution was not made with all of this group of patients; however, a previous clinical trial with indomethacin tablets and placebos demonstrated a highly significant drug-placebo response difference.[10]

Results

With most patients who obtained a favorable response medication was stopped on one or more occasions, usually with a prompt loss of improvement. The composite grading scale used was as follows: excellent response indicates over 50 percent clinical improvement; good, 25 to 50 percent improvement; fair, 10 to 25 percent improvement; and poor, less than 10 percent improvement.

Table 1 gives the over-all results in the patients given indomethacin. About 50 percent of the patients with peripheral rheumatoid arthritis reported a good or excellent response to the drug, with benefit usually evident in 24 to 48 hours. Most patients reported their improvement in terms of decreased joint pain, decreased morning stiffness, and increased ease in walking, getting out of a chair, or dressing themselves. Objective lessening of joint swelling and tenderness was less evident, and significant decreases in sedimentation rates occurred in only a minority of patients. Many were able to stop or greatly reduce their salicylate intake and several on adrenal corticosteroids were able to reduce their dosage by 25 to 50 percent.

Of seven patients with rheumatoid spondylitis, or rheumatoid spondylitis with peripheral joint involvement, all reported a good or excellent response to indomethacin. This greater effectiveness of indomethacin in the atypical forms of rheumatoid disease is also a characteristic of the action of phenylbutazone.

Toxicity

Table 2 summarizes the adverse reactions observed while patients were taking indomethacin.

Gastrointestinal

Seven patients reported some symptoms of gastrointestinal irritation; two developed severe nausea and had to discontinue medication; four reported mild nausea or epigastric burning. In all of these patients, however, symptoms disappeared with the passage of time or with a slight reduction in dosage. One patient, whose pretherapy gastrointestinal X ray was normal, was found to have a small gastric ulcer after 12 weeks of indomethacin, on a dosage of 100 mg. per day. She was without symptoms, and on initiating an ulcer regimen and stopping indomethacin the ulcer healed two weeks later. This patient had been under considerable family stress at the time the ulcer was discovered. Of interest is the fact that two other patients demonstrated peptic ulcers on their pretherapy routine X rays. They were without symptoms and were continued on indomethacin, 150 mg. per day. X rays one and two months later, respectively, demonstrated healing of both ulcers.

Headache

Twenty-two patients reported head symptoms, usually headache, dizziness, vertigo, or light-headedness. In ten these symptoms were mild and disappeared either spontaneously or following a slight reduction in dosage. In eight patients these symptoms were classed as moderate; but in all instances the headache was controlled by a reduction in dosage or with the addition of an antihistamine at bed time. Four patients had severe headache, especially evident in the morning, and they refused to continue indomethacin. One of these patients was taking 150 mg. per day, one 100 mg. per day, and two were taking only 75 mg. per day. Gross fluid retention was not observed with indomethacin, and there was no relationship of headache to the occasional slight weight gain that occurred in a few patients.

Skin Rash

One patient who had been on indomethacin for ten weeks on a dosage of 150 mg. per day developed severe itching and a moderate, diffuse, raised erythematous rash over his arms and trunk which disappeared promptly on cessation of the drug.

Laboratory Studies

In addition to the usual routine laboratory procedures, liver profiles (serum bilirubin, alkaline phosphatase, zinc and thymol turbidity, cephalin flocculation, serum electrophoresis, SGOT) were done at regular intervals on all patients taking indomethacin. No significant abnormal laboratory changes occurred, with the exception of one patient who developed neutropenia. This patient was a 64-year-old male with rheumatoid arthritis. He received tablets of indomethacin for fourteen months and capsules of indomethacin for an additional week. The dosage was mostly 150 mg. per day but varied from 50 to 200 mg. per day. The clinical response was good.

TABLE 1
Overall Clinical Response to Indomethacin

Disease	Number of Patients	Good or Excellent	Fair	Poor or No Response
Rheumatoid arthritis	54	26	14	14
Rheumatoid spondylitis	4	4	0	0
R.S. plus peripheral R.A.	3	3	0	0
Total	61 (100%)	33 (54%)	14 (23%)	14 (23%)

TABLE 2
Toxicity to Indomethacin in 61 Patients

Nature of Side Effect	Severe Reaction	Moderate Reaction	Mild Reaction	Total Number
Gastrointestinal	3	0	4	7 (11%)
Headache, vertigo, etc.	4	8	10	22 (36%)
Skin rash	0	1	0	1
Neutropenia	0	1	0	1

His initial pretherapy total white blood cell count was 7,800 with a differential count of 78 neutrophiles and 22 lymphocytes. The first definite change was in the thirty-second week when the total WBC was 4,525 with 54 neutrophiles, 32 lymphocytes, 8 monocytes, and 4 eosinophiles. During the next 23 weeks frequent checks of the WBC gave values of 3,650 to 4,900 with the neutrophiles ranging from 22 to 55 percent. In the sixtieth week of indomethacin therapy the WBC was 3,200 with 18 neutrophiles, 47 lymphocytes, 12 monocytes, and 21 eosinophiles. Indomethacin was discontinued in the sixty-first week, and two weeks later the WBC was 5,050 with 37 neutrophiles, 44 lymphocytes, 7 monocytes and 12 eosinophiles. Thereafter the neutropenia progressively improved.

Selected Case Histories

Case No. 1

A 60-year-old male with rheumatoid spondylitis of 25 years duration and a history of iritis and a duodenal ulcer was placed on indomethacin capsules, 50 mg. twice a day. Within two days there was a 50 percent decrease in back stiffness and pain. For the past eight months the patient has continued on 50 mg. to 100 mg. of indomethacin per day with a progressively good response. Several attempts at stopping the medication, or the substitution of placebo therapy, caused a flare in his symptoms. Laboratory studies during this period indicated no significant change in hemoglobin, sedimentation rate, urine, or various liver function tests. There have been no gastrointestinal symptoms.

Case No. 2

A 43-year-old female with rheumatoid arthritis of 17 years duration was started on indomethacin tablets in August, 1962, at a dosage of 200 mg. per day. The patient had excellent relief of joint pain with objective reduction in joint swelling; however, headaches, especially in the morning, were a disturbing feature. On reduction of the dose to 150 mg. per day, the frequency of morning headache was decreased. After ten months the patient was transferred to indomethacin capsules, continuing for the next eight months. On a dosage of 150 mg. per day she was essentially free of morning headaches and able to continue her usual housework schedule. Several attempts at placebo substitution resulted in a prompt return of joint symptoms, but there also was the disappearance of the minimal a.m. light-headedness which the patient occasionally had while on indomethacin. The sedimentation rate decreased from an initial value of 105 to a current level of 85 millimeters in one hour (Westergren); all other laboratory tests are normal.

Case No. 3

A 60-year-old white female patient with rheumatoid arthritis of two years duration had been given two trials of phenylbutazone, 300 to 400 mg. per day, without significant improvement in her joint symptoms. On April 24, 1963, she was started on indomethacin 50 mg. three times a day. Within 48 hours there was a 50 percent improvement in her joint symptoms; but beginning on the third day the patient also noticed morning headache which took about one to one and a half hours to disappear. Objectively, there was a significant decrease, from a grade two to a grade one, in the swelling and tenderness of her knees, wrists, and metacarpal-phalangeal joints. The medication was continued at the same dosage level despite the morning headache, and by the end of the second week the headache disappeared except for occasional mild discomfort, especially if she delayed eating her breakfast. After six weeks the indomethacin dose was reduced to 50 mg. twice a day. Both the subjective and objective improvement initiated by the higher dosage of indomethacin was maintained on the lower dose, and the patient was now completely free of morning headache. Except for several brief periods of stopping indomethacin, which were promptly followed by an increase in joint pain, and an increase in wrist and finger swelling and tenderness, the patient continued to do very well thirty-six weeks later. She estimates a 75 percent improvement in her arthritis. At the start of therapy the sedimentation rate was 78 mm. in one hour (Westergren), and it showed a progressive decrease to 21 mm. Other laboratory data, including liver function, renal function, and X rays of the stomach, remain normal.

Summary

In a group of sixty-one patients with rheumatoid arthritis or rheumatoid spondylitis over 50 percent demonstrated significant clinical improvement in their disease following administration of a new anti-inflammatory agent, indomethacin, in a dosage of 75 to 200 mg. per day. Five percent of the patients developed significant gastrointestinal upset; however, the major toxic symptoms were headache, vertigo or light-headedness. In most instances these symptoms were capable of being controlled with a reduction in dosage of the medication. It is apparent that some patients cannot tolerate the drug, and the development of side effects will exclude its use in perhaps ten percent of patients. Indomethacin represents a new type of compound which may offer considerable help in the management of rheumatoid arthritis and more especially, rheumatoid spondylitis.

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STURGE-WEBER SYNDROME

This syndrome has a large variety of synonymous terms. It is particularly characterized by vascular nevi of the face, scalp, trunk, extremities and the leptomeninges. It is considered to be congenital and inherited as an irregular dominant characteristic.

There are cutaneous angiomas and these may be telangiectatic or cavernous, having the color of a port wine stain. They sometimes occur along the distribution of the trigeminal nerve. The angiomas sometimes extend into the underlying fat, muscle, and bone, or they may be found at post-mortem in the lungs, thymus, spleen, testes, lymph nodes, and in the pituitary gland.

Intracranial angiomas occurring in the leptomeninges may cause neurologic manifestations, contralateral hemiparesis, hemiatrophy, Jacksonian epilepsy, and mental retardation.

X-ray examination of the skull may reveal calcified angiomas or localized linear calcification outlining the cerebral convolutions.

Successful therapy is limited to small cutaneous lesions.

Durham—Encyclopedia of Medical Syndromes, Hoeber, Inc.

WHAT'S YOUR DIAGNOSIS?

A fifty-five-year-old white female was seen in the emergency room with sudden pain and numbness of the left lower leg and foot of two hours duration. There had been no trauma. She was not under a doctor's care.

Pertinent physical examination indicated an obese female in moderate discomfort. The chest was clear. The heart had an irregularity of the rhythm and an apical systolic and diastolic murmur. The left leg, below the knee, was pale and without motor or sensory power. The arterial pulse was present high in the left groin, questionably in the popliteal area, and not in the foot. The right femoral arterial pulse equaled the left and pulses were weakly present in the right foot and popliteal area.

What's Your Diagnosis? Turn to page 786

Middle Age

A man is middle-aged when he realizes he can't do as much work as he once could do . . . if he'd done it.—Marcelene Cox, Ladies' Home Journal

The Acute Abdomen

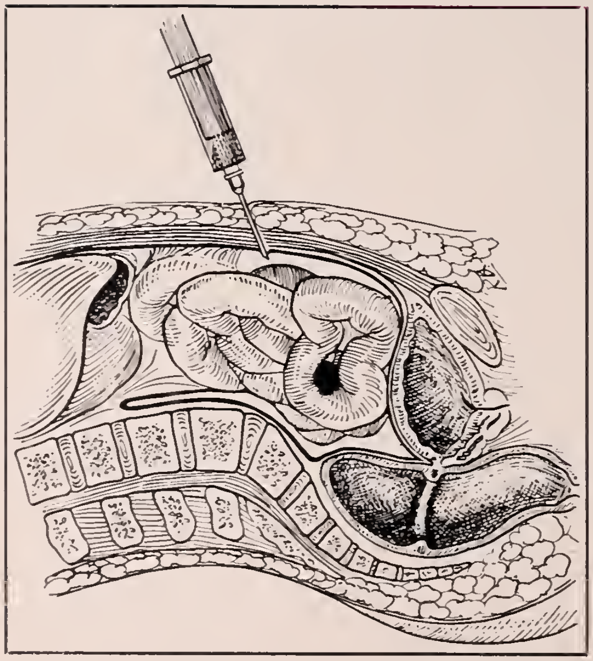

Fig. 1 — Diagnostic paracentesis. A needle can be inserted safely through the abdominal wall in any area free of adhesions. The layer of telltale fluid may be very thin against the parietal peritoneum.

When a doctor faces an acute abdominal problem, he accepts a challenge to his completeness as a physician. Diagnosis only begins his problem. He must relate the present illness to the whole patient, considering previous diseases, medications, and allergies, and recognizing any hidden handicap in vital functions; he must further identify all components of disturbed physiology, and judge their gravity and their rate of change. Only then can he attempt in proper priority to restore each deranged function. A surgical procedure may accomplish some necessary, specific purpose, but will never be more than a part of the mosaic of ideal treatment.

Extrapolation of the patient's course into the next several hours will indicate the urgency of each step in therapy. While we gain ground in one parameter, we may lose it in another, as the clock runs on. The net balance for better or for worse is a valuable test of the therapeutic plan.

Diagnostic Paracentesis

Ischemia, bleeding, and peritoneal contamination are primarily surgical conditions; each begins and continues with ever-heightening risk. Sometimes the physician may be

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sorely taxed to decide the nature of disease in the acute abdomen; he may reach security of decision only after diagnostic paracentesis (Fig. 1). There is little risk in inserting a needle into the abdominal cavity, provided one avoids incisional scars. With great care and delicacy, it may be possible to aspirate abdominal fluid from the thin layer lying against the parietal peritoneum. Only a few drops suffice to indicate the presence of blood, pus, or serous effusion.

Purposes of Surgical Procedure

A surgical procedure may accomplish any of the following therapeutic objectives:

Secure Bleeding

The more rapid the bleeding, the more urgent is surgical control (ulcer, trauma, ectopic pregnancy). Paradoxically, the presence of associated cariovascular disease may make operative treatment more urgent, as the diseased heart will stand surgical stress better than it can tolerate the hypoxia of anemia and shock. The therapeutic objective of an operation is simply the control of bleeding. A major definitive procedure may be required. Such a procedure can be done with less risk

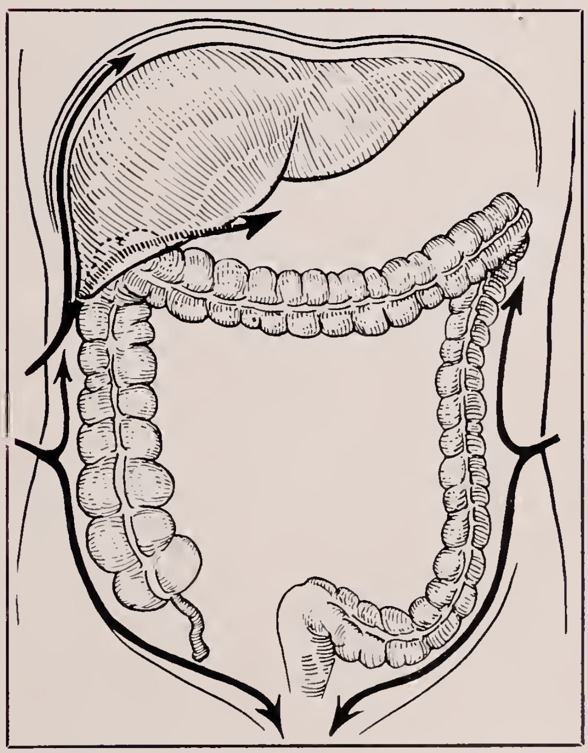

Fig. 2 — Although the general peritoneal cavity cannot be drained, preferential sites of fluid accumulation and potential abscess formation can be drained. These are the pelvic space, both gutters, and the subhepatic and suprahepatic spaces.

when done early in the course of bleeding, before blood volume has been lost and replaced again and again. Multiple transfusions bring problems of their own, including acidosis, hemolytic reactions and coagulation defects; therefore, transfusion and surgical control of bleeding must be planned and carried out together, in order to restore functional integrity and normal blood volume with the least total danger to the patient.

Secure Source of Peritoneal Contamination

(Perforated viscus, bile peritonitis.) Continuing contamination rapidly produces established, invasive sepsis, with all its sequelae. It is urgent that the source of contamination be removed, sealed, or exteriorized. Time is critically important.

Provide Drainage

Aspiration of irritating or infected peritoneal contents diminishes toxicity. Subsequent abscess formation may be prevented by drainage (Fig. 2). The peritoneal cavity as a whole cannot be drained, but sites of accumulation can be drained, especially the pelvic cul-de-sac, the two gutters, and the right subphrenic space. Adequate drainage requires a loose passageway along the drains and through the abdominal wall. Solitary collapsible tubes drawn through tight stab wounds do not suffice.

Restore Organ Function

Vascular: Removal of thrombus or embolus from the superior mesenteric artery is successful only within a very few hours of onset. The danger of gangrene demands the early surgical treatment of intestinal obstruction.

Gastrointestinal: In addition to relief of obstructing mechanisms, the surgeon can promote early return of gastrointestinal function by judicious decompression of distended loops of bowel; by plication of raw surfaces; and by careful handling and orderly replacement of intestinal loops. Precise surgical technique in all maneuvers is essential.

Other: Other organs, especially the biliary tract, may require correction under difficult circumstances. The selection of the best operative procedure may tax the surgeon's experience and originality.

Remove Disease

Primary definitive surgical treatment is being extended after successes with emergency gastrectomy, emergency aortic resection, and the surgery of trauma. The best procedure is always the safest one under the circumstances at hand.

Derangements in Physiology

Fluid and Electrolytes

Depletion of fluids and electrolytes is a common derangement in the acute abdomen. Fluid is visibly lost as urine, diarrhea, vomiting, and sweat; large quantities may be invisibly lost in sequestered edema and distended intestinal loops. Rapid derangement of hydrogen, sodium, potassium, and chloride ionic concentrations develops; changes which have profound effects on muscular strength and intestinal, cardiac, and renal functions. These derangements are dynamic, increasing with increasing disease and leading to weakness, mental confusion, oliguria and collapse. Such a patient cannot tolerate anesthesia and surgery until he is restored.

Remedial Measures

Remedial fluid treatment must be accurate in volume and in constitution. First attention to plasma volume justifies the use of plasma expanders, but excessive dilution of remaining body electrolytes must be avoided. Dextrose in normal saline should be given until urinary excretion exceeds 50 cc. per hour. Potassium chloride should then be added in the amount of 40-100 mEq. per day. Initial volume estimates of three per cent of body weight for moderate depletion, or six per cent of body weight for severe depletion of water are helpful, but initial estimates must be subject to change. Observation of appearance, skin turgor, mental status, hourly urinary output, and serum electrolyte concentrations will guide treatment. The immediate therapeutic objectives are limited: to restore diuresis and to direct electrolyte composition toward normal. Complete restitution is neither likely nor necessary in early phases.

When restoration is well begun, and diuresis starts, operative treatment can be undertaken.

Plasma Volume

Extensive inflammation, as with peritonitis, causes profound changes in plasma volume, in the range of 500 to 2000 cc. These represent direct losses of plasma sequestered in the tissues as obligatory edema. With compensatory changes and water treatment, plasma proteins are further diluted; significant loss of colloid osmotic pressure is an important result. Elevation of hemoglobin and hematocrit indicate the extent of plasma loss.

Therapy

The therapeutic objectives are to replace plasma volume and to maintain colloid osmotic pressure.

Choice of Fluids

Several products are available. Normal saline solution has a beneficial but transitory effect, as it passes promptly through capillary walls into the interstitial fluid. Dextran solution stays longer in the plasma space; but as commercially available, it has little effect on colloid osmotic pressure. Human pooled plasma fulfills both objectives and is readily available at a cost of approximtely $20 per 300 cc. unit. If it has been irradiated with ultraviolet and stored at least six months at 88° F, it is free of hepatitis virus and can be used with safety. Preparations of human serum albumin are also available in 5% concentration in saline solution or in 25% salt-free solution. These preparations cost more than plasma per unit, but less than plasma per gram of albumin. It is the albumin which helps to plug the exudative leak and draw edema fluid back into the capillaries. Intensive use of plasma and albumin is costly treatment but nearly specific for this important physiologic disturbance in peritonitis.

Hemorrhage may be an important component of the physiologic disturbance in the acute abdomen, as it takes its toll by impairment of perfusion of body tissues, with resulting anoxia, anaerobic metabolism and acidosis. The critical tissue is often the kidney, where tubular necrosis may occur. The therapeutic objective is to maintain tissue perfusion, not to treat the blood pressure. The patient with acute hemorrhage has already contracted his blood-vessel volume as much as he can by sympathetic nervous system discharge, and by the secretion of adrenalin and noradrenalin. Little or nothing can be accomplished by the addition of higher blood levels of these hormones in synthetic form. What is needed is fluid for the pump. The most appropriate fluid is whole blood, properly prepared in a reliable laboratory. In emergency, while blood is being prepared, support to the blood volume can be given by any intravenous fluid: plasma, albumin, dextran, or even normal saline. The therapeutic objective is replacement of blood volume to normal.

The Use of Blood

It is often difficult to judge the amount of blood required, and the dangers of under-transfusion and over-transfusion are equally grave (Fig. 3). Safe management requires aggressive administration of as much blood as is necessary to restore normal circulation. Good perfusion of tissues is indicated by full pulse volume, by dry, warm skin, and by hourly diuresis in excess of 30 cc. Protection against over-transfusion requires repeated measurement of central venous pressure to detect impending cardiac failure. This measurement can be conveniently made via a side-

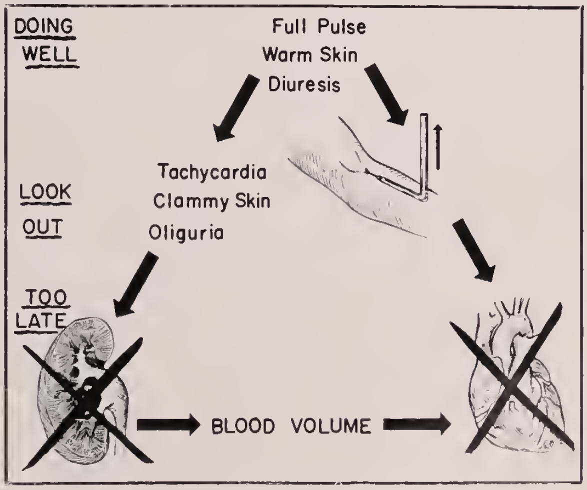

Fig. 3 — The dangers of under-transfusion and over-transfusion are equally grave. Warning signs are available for the alert physician who observes his patient, records hourly urine output, and monitors venous pressure.

arm from the transfusion apparatus. Any acute rise in venous pressure provides an early indication of over-transfusion.

Antibiotics

Sepsis is a dreaded component in the acute abdomen. Surgical control of contaminating sources, and free external drainage may deprive infection of invasiveness and allow body defenses to prevail. Antibiotics are exceedingly important here. They should be used in heavy dosage for as long as the tendency to invasive infection persists. Choice of agent should be guided by culture studies. My usual initial preference is for massive intravenous doses of penicillin (4 to 12 million units daily) in conjunction with intravenous or intramuscular chloramphenicol (2 gm. daily).

Other Derangements

Further, the complete physician will be alert to other derangements of function. Abdominal distention, or just abdominal pain, can compromise respiratory excursion. Tracheobronchial toilet must be maintained by coughing and deep breathing, and by special measures. Carbohydrate and vitamin therapy protect liver function. Artificial control of body temperature may be helpful. The subject of shock exceeds this paper in scope, but is germane to the problems of the acute abdomen. The integrated management of late peritoneal sepsis, with profound catabolism and deteriorating bodily functions, represents the ultimate challenge to the concept of complete, physiologic care.

Summary

Whatever the kind of acute abdominal disease, a series of disturbances is produced in multiple functions of the body. The physician must identify all of these disturbances, judging both their magnitude and their rate of change. He must establish in his mind the relative importance of each one and the best way to treat it. Ideal treatment of the patient is the sum of therapeutic steps, possibly including a surgical operation, taken accurately and in proper priority, to return the patient to normal functional integrity.

ANSWER TO WHAT'S YOUR DIAGNOSIS

(From page 781)

Rheumatic heart disease with mitral valvular lesion, auricular fibrillation, and peripheral embolus to bifurcation left femoral artery.

How to Set a Broken Nose

Medical science in Egypt, recorded in hieroglyphics on papyrus, briefly directs the doctor faced with a broken-nosed patient to proceed thus: "Thou shouldst cleanse it for him with two plugs of linen. Thou shouldst place two other plugs of linen saturated with grease in the inside of his two nostrils. Thou shouldst apply for him stiff rolls of linen by which his nose is held fast. Thou shouldst treat him afterward with lint every day until he recovers." — Still good 5000 years later, this procedure should afford us a rare sense of kinship and rapport with our ancient Egyptian and Greek colleagues.

A good many people can make a speech, but saying something is more difficult.
—Herbert Prochnow

Missed Abortion

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THE EXACT incidence of missed abortion is hard to assess. Review of the literature on the subject would suggest that it is a relatively infrequent problem in general obstetrical practice. The incidence of ante-partum intra-uterine fetal death has been statistically studied by several authors. Dippel,[1] for example, found on reviewing 25,000 deliveries at Johns Hopkins Hospital, that in 302 cases, or 1.22%, fetal death had occurred prior to labor and the emptying of the uterus; Triconi and Kohl,[2] in studying 19,067 deliveries, found an incidence of 1.03% of ante-partum fetal death. In most of these cases the exact time of ante-partum death of the fetus could not be ascertained.

Experiences in consultation obstetrical practice have demonstrated that the occurrence of the retention of the product of conception after death of the fetus is much more frequent than the literature would suggest. The diagnosis of missed abortion is not made in many instances because of a reluctance on the part of many physicians to examine a patient who is bleeding, because of the fear of introducing infection or increasing the probability of spontaneous abortion. This failure to perform a pelvic examination on a bleeding pregnant patient for fear of interrupting a pregnancy is unjustified in my experience, and the early diagnosis of missed abortion becomes more important since the recent reports by many writers of occasional complicating afibrinogenemia in this condition.

Diagnosis

The diagnosis of fetal death in which there has been intra-uterine retention long enough to qualify as a missed abortion can best be made on the basis of lack of increase in the size of the uterus. In many instances, a definite decrease in the size of the uterine corpus will be noted. In more advanced pregnancies, disappearance of fetal heart tones or X-ray changes suggestive of intra-uterine fetal death may be helpful in establishing a diagnosis. Occasionally a negative pregnancy test may give confirmatory evidence of fetal death. Subjective disappearance of fetal motion, as noted by the patient, will help in determining the length of time the fetus has been dead.

Fibrinogen Defects

It has been customary to teach that conservative expectant treatment of missed abortion should be followed. In recent years, since the description by Duncan Reid[3] of afibrinogenemia with abnormal bleeding as a complicating factor in long-standing intra-uterine fetal deaths, more active intervention has been suggested by some, rather than a prolonged period of "watchful waiting." Fibrinogen depletion of a degree sufficient to cause abnormal bleeding has been described as occurring as a complication of pregnancy in abruptio placentae, in intra-uterine fetal death with prolonged retention of the fetus, and in amniotic fluid embolism. Much less commonly, it may occur in three other conditions: septic abortion, fulminating eclampsia, and retained placenta.[4] In those instances associated with missed abortion there may occasionally be a striking depletion of fibrinogen, and possibly some reduction in prothrombin activity, although the change in prothrombin time is rarely, if ever, sufficient to reach hemorrhagic levels. Fibrinolytic activity has not been demonstrated. Weiner and Reid and others[5] have suggested that the fibrinogen depletion is probably due to thromboplastic material from the uterine contents gaining access to the maternal circulation and causing intravascular coagulation with abnormal consumption of the fibrinogen.

Case Report

The following case of missed abortion is illustrative of the management problems of abnormal bleeding complicated by failure of the clotting mechanism due to fibrinogen depletion.

A female patient, aged 31, was admitted to The Charles T. Miller Hospital, Saint Paul, on November 17, 1956, and discharged on November 24, 1956. The patient, a para 3-0-0-3, stated that her last menses had begun August 26, 1956. She had developed painless vaginal bleeding five days before admission to the hospital and had noted chills and fever the night before admission with a temperature elevation to 104°. Examination at the hospital revealed a few moist rales in right chest and a nontender corpus the size of a sixteen weeks' pregnancy as the only significant findings, aside from a temperature elevation of 103° and a white blood count of 11,250 with 92% PMN's. The chest X ray was negative; cultures from throat and cervix both revealed alpha streptococci; a blood culture drawn prior to treatment with intravenous and oral tetracyclains was negative. The patient made an uneventful recovery and was followed for several outpatient visits, reporting on each occasion the continuance of moderate vaginal bleeding.

On December 27, 1956, she passed a small portion of macerated fetus. She was readmitted to the hospital on January 4, 1957, because of sudden, rather profuse bleeding. Examination at this time disclosed a vagina filled with clotted blood, and a uterus again described as the size of a sixteen weeks' pregnancy. Admission hemoglobin was 12.9 gm. with 12,800 white blood count.

Because of the amount of bleeding, a curettage was attempted the night of admission. Very profuse bleeding developed during the curettage and rather profound shock occurred, even after the rapid administration of four units of whole blood. Very firm packing of the curetted area failed to stem the bleeding, and hysterectomy was decided upon. At this point it was noted that the blood escaping from the vagina failed to clot. Over the next hour the patient received two grams of fibrinogen with restoration of normal clotting. Abdominal hysterectomy was rapidly carried out, the patient receiving two more grams of fibrinogen and a total of thirteen units of blood during the course of the curettage and the hysterectomy. Her hemoglobin stabilized at 12.5-13 grams during the next two days. The explanation for the failure to control the hemorrhage by curettage and packing was immediately apparent once the abdomen was opened. The patient had had an unsuspected cervical pregnancy. Following the total abdominal hysterectomy and multiple transfusions, she made an uneventful recovery and was discharged on her eighth hospital day.

Pathologic Report

Sections taken from a large, flabby cervix showed evidence of chorionic villi, most of which were necrotic and related to a decidual reaction against the cervical wall. Associated with the material was blood clot, some of which appeared to be undergoing disintegration. There was minimal cellular reaction in the cervical wall adjacent to the placental site.

There are several points about fibrinogen depletion associated with missed abortion which should be emphasized to the physician faced with the problem of managing this condition. These points have been most aptly expressed in an article by Pritchard.[6] Plasma levels of fibrinogen rarely fall to dangerous (i.e., 150 mgm. percent) levels in less than five weeks after intra-uterine fetal death. It should be noted that a fibrinogen level of 150 mgm. per 100 ml. is considered ample for effective blood coagulation during pregnancy and the puerperium. The drop in fibrinogen level is usually slow and progressive, descending in linear fashion. In only one instance was there a rather precipitous drop over a period of a week; also in only one case was there spontaneous correction of a hypofibrinogenemia noted during pregnancy. Fibrinogen administration without emptying the uterus is worthless, since its use results only in a transitory elevation of the circulating fibrinogen. Moreover, the administration of fibrinogen is not without some danger, since two of nine cases in which it was used developed a homologous serum hepatitis.

Treatment and Conclusions

Treatment of missed abortion should still remain conservative and expectant. The overwhelming majority of patients will evacuate the uterus spontaneously if sufficient time elapses after death of the fetus. Triconi and Kohl pointed out that by the end of the third week following death of the fetus all but seven percent had emptied the uterus. In the event that retention of the dead products of conception persists longer than five weeks, one should be cognizant of the possibility of fibrinogen depletion, and while conservatism should still be practiced, periodic fibrinogen levels should be noted. Active interference should be reserved for those few patients who asymptomatically drop their plasma fibrinogen levels below 150 mgm./100 ml. blood, or in whom there is a clinically demonstrable failure in hemostasis at a somewhat higher blood fibrinogen level, i.e., gingival bleeding or bleeding into the muscle following slight trauma at fibrinogen levels of 200 mgm./100 ml.

The method to employ in attempts to empty the uterus depends mostly upon the size of the uterus at the time interference is required. In those instances in which the uterus is no larger than two-and-a-half to three months' gestation, active treatment by dilation and curettage can be instituted at any time. In uteri which are larger than this, one should depend primarily upon the intravenous infusions of oxytoxic materials. Repeated courses of intravenous pitocin or syntocinon[7] may be required before evacuation of the uterus is accomplished. Recently Maclure and Ferguson[8] have reported on the use of relaxin as an adjunct in the use of pitocin infusions. On rare occasions laparotomy may be required in those instances with failure of hemostasis where evacuation of the uterus cannot be accomplished by more conservative means. A case in point is cited.

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CRUVEILHIER'S SIGN
(Sapheno-femoral Varix)

A small compressible mass in the femoral region may be a femoral hernia or it may be an aneurysmal dilatation of the saphenous vein. When the patient coughs there is a sensation as if a jet of water is entering and filling the saphenous pouch. This is called Cruveilhier's sign. This is palpable with the fingers and differentiates between a femoral hernia and a varix of the saphenous vein.

People are usually willing to meet each other half way, but their judgments of distances vary considerably.—The Rodney (Ont.) Mercury

Aganglionic Megacolon

Current Surgical Treatment

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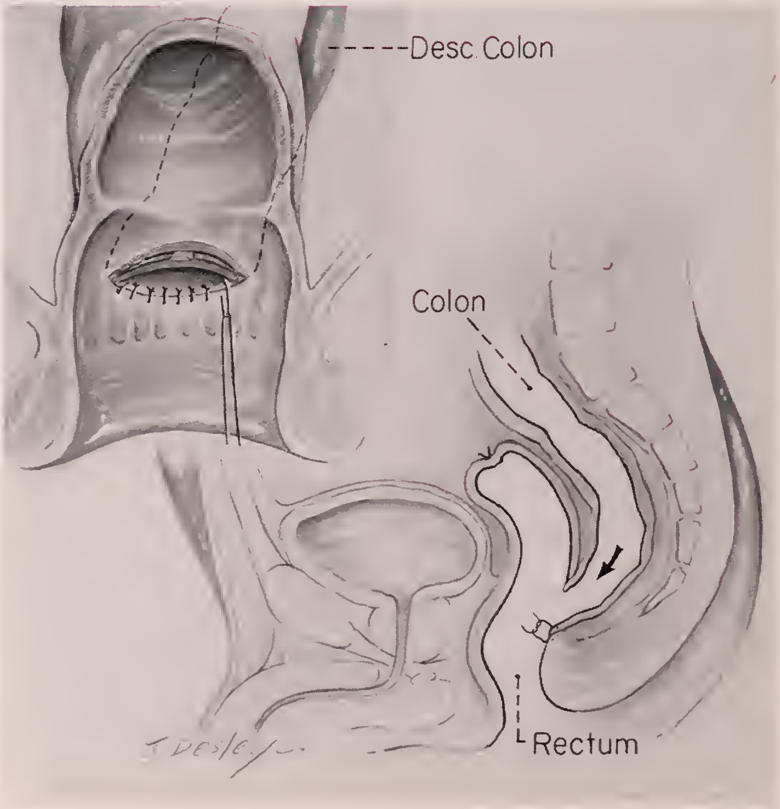

Fig. 1 — Normal colon has been brought down posterior to blind rectal pouch and through incision above anal sphincters. Posterior edge of colon is being sutured to inferior edge of rectal incision.

FOR MORE than 15 years Swenson's operation has been the accepted definitive treatment for aganglionic megacolon, and complications have been fairly numerous. The major cause of the difficulties has been the pelvic dissection necessary to resect the upper portion of the rectum. In 1957 Duhamel[1] described a modification of the Swenson procedure that virtually eliminated this extensive pelvic dissection. His procedure consisted of forming a blind rectal pouch and then bringing the normal colon down posterior to this and out between the internal and external anal sphincters. The wall between these segments of bowel is then divided with spur-crushing clamps. Grob[2] modified this procedure slightly by bringing the proximal segment of colon out through the posterior wall of the rectum above the sphincter. It is this modification that we have used since May 1962.

Procedure

A brief description of the procedure is as follows. The child is prepared for surgery with cleansing saline enemas. Penicillin and streptomycin are given the morning of the operation. The patient is placed on the operating table in the lithotomy position. An indwelling catheter is placed in the bladder, and intravenous fluids are started. The abdomen is prepared and draped for both abdominal and perineal operations.

Abdominal Portion

An oblique skin incision is made beginning in the left flank and extending below the umbilicus across the midline. Abdominal exploration is then carried out to determine the amount of colon to be resected. The site of distal division of the colon, where the end is to be closed to form the blind rectal stump, has been chosen for the convenience of the surgeon and not in relation to the presence of ganglion cells. The proximal line of resection must be at a level where ganglion cells are present, and it is usually best to resect the markedly hypertrophied segment of bowel if this does not necessitate the removal of too much colon. The colon is then freed up so that this segment may be removed and so that the proximal end of the remaining colon will reach to the anus. Needless to say, the blood supply to this end must be preserved. The bowel is then resected. The rectal stump is closed in two layers. The proximal end is temporarily closed with a running catgut suture.

Blunt dissection can then be used to make a channel posterior to the rectum. When the channel reaches the area where the colon will be brought through into the rectum, the abdominal part of the operation is finished.

Perineal Portion

The surgeon then begins the perineal part of the procedure. An incision is made in the posterior wall of the rectum about 1 cm. above the dentate line and is extended about one third of the way around the circumference of the rectum. It is carried down through all layers of the rectal wall. An assistant's finger may be inserted into the channel from above to help identify the desired depth of the incision. A curved clamp is then passed up through this opening, and the proximal portion of colon is pulled through so that the mesenteric border is posterior. The temporary suture closing the colon is removed. The posterior edge of the colon is sutured, with interrupted catgut sutures, to the inferior edge of the incision made in the rectum (Fig. 1). Ochsner clamps are then used to crush the spur. They are applied in such a manner that the final stoma will be triangular in shape with the apex superior (Fig. 2). An incision is then made in the devitalized area. Although this incision is not necessary for the final result, it allows for easier escape of gas and feces before the clamps fall off, and also probably allows the clamps to come off a day or so sooner.

The abdomen is then closed; it has not been found necessary to use drains.

Postoperative Care

Postoperatively some means must be used

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to protect the large clamps that protrude from the rectum. We have found Bryant's traction, or similar leg traction, satisfactory in this regard. Older children are usually kept in traction only one to two days and then are ambulated in an almost normal fashion, except that it is impossible for them to sit while getting up. Younger children have been kept in traction until the clamps have fallen off. The clamps usually fall off in seven days. In one case clamps with detachable handles were used to eliminate the disadvantage of protruding clamps; but the clamps were technically unsatisfactory and allowed the colon to retract, leading to many complications, as will be mentioned later. This unfortunate case has discouraged us from attempting to make another clamp until we are satisfied with the procedure itself. The indwelling cathether is left in place until after the clamps have fallen off. Use of penicillin and streptomycin is continued postoperatively.

Results

To date, eight patients have been managed with this procedure. There were seven boys and one girl, and their ages ranged from 14 months to 15 years. These patients are all functionally improved at this time; none require enemas. Four patients are old enough to be toilet-trained; three have no significant soilage; one, a six-year-old, has slight soilage, but this does not require wearing a pad or changing underclothes. In further evaluating this procedure, each case must be evaluated for possible complications related to this technic.

Complications

The first patient had a left pleural effusion caused by a technical problem associated with threading a catheter in the basilic vein for administration of fluids.[3] The vein ruptured into the pleural cavity with fluids going directly into the pleural space. This complica-

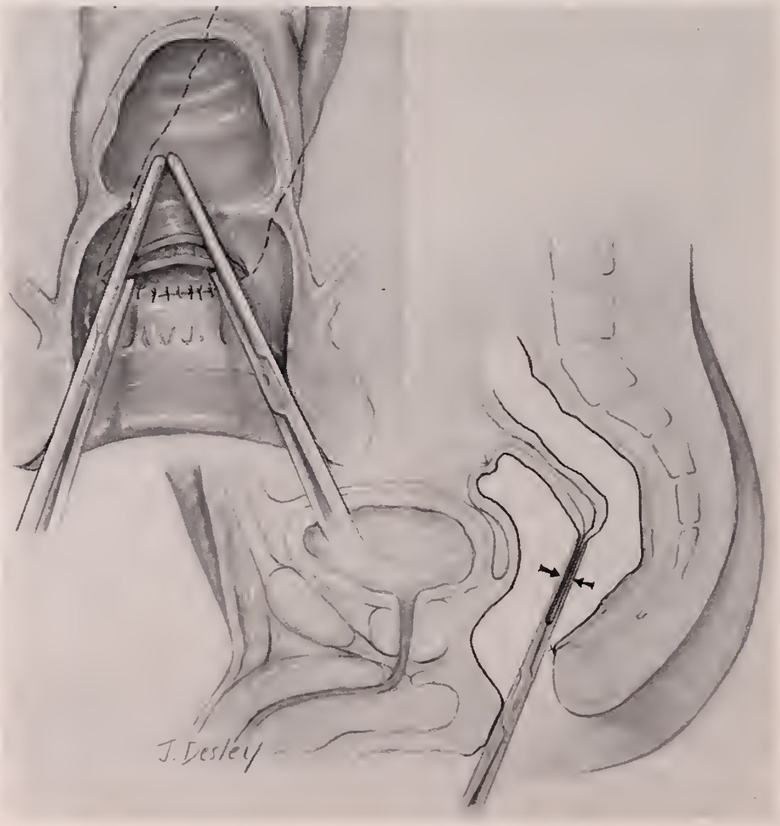

Fig. 2 — Ochsner clamps are applied to crush spur.

tion was therefore not related to the procedure.

Peritoneal Contamination

The second patient is the one for whom the clamps with detachable handles were used. The clamps slipped, thereby allowing retraction of the proximal portion of bowel with spillage of feces into the peritoneal cavity. A second operation was required. The abdomen was drained, a diversional colostomy was performed, and the anastomosis was redone, again with the use of clamps. The patient recovered, but the anastomotic stoma was too small and a fecal fistula developed. At the third operation clamps were reapplied and the fistula was excised. The stoma is now adequate but the fistula has recurred. At the fourth operation the colonic stoma was closed. A small fecal fistula, which intermittently drains, is still present.

The third patient had most of his colon resected and has about five stools daily but no other complaints.

The fourth patient experienced no complications.

Bleeding

The fifth patient, who had an ileoproctostomy for aganglionosis of the entire colon, has five to six stools daily and has had an anal fissure. Postoperatively, he had an episode of upper gastrointestinal bleeding which is thought to have been caused by a stress ulcer.

The sixth and seventh patients had no complications.

The eighth patient had significant rectal bleeding requiring 1000 ml. of blood the day after the clamps fell off; she had bleeding into the abdominal wound at the same time. (There was also a history of bleeding on the eighth day following her colostomy, which was performed elsewhere.) This complication could well have been due to an unexplained bleeding disorder, which was studied before operation by the hematology service.

Comments

Only one patient (Case 2) had complications that can be directly related to this procedure, and these were associated with the faulty clamps rather than with the procedure itself.

One complication which it was thought might develop was inertia of the bowel because of the blind rectal stump. This has not occurred. In the case of aganglionosis of the entire colon, the blind stump included the colon back to the mid-transverse colon. This long segment was left in the event that the patient had excessive diarrhea, in which case reanastomosis to the colon higher up might be necessary. However, no complication has occurred.

One point should be made in regard to preliminary colostomy. If the length of anticipated resection can be determined at time of colostomy, the colostomy should be made just proximal to this point. At the definitive operation, the proximal resection can be made just proximal to the region of the colostomy, and thus the necessity for closure of the colonic stoma is eliminated.

Summary

The modified Duhamel procedure has been a satisfactory operation which is relatively easy to perform and should not be associated with many complications. However, it is too early to make a final appraisal or to recommend it to replace the Swenson procedure.

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Happiness is that peculiar sensation you acquire when you are too busy to be miserable.—Mutual Moments

IT'S THE LAW*

Legal Evidence of Causal Connection Between Trauma and Cancer of the Breast

In a personal injury suit by a woman against a store for damages for injuries received from a fall while shopping, there was sufficient evidence of causal connection between injuries received in the fall, and cancer which subsequently developed, to raise a question for the jury, the Minnesota Supreme Court ruled.

Two days after her fall, the woman observed a bruise, a black and blue mark, on her left breast. The bruise remained for some time, then turned yellow, and finally disappeared. She continued, however, to observe pain in her left side and in her left breast.

Fourteen months after the original injury she observed for the first time a large lump in the breast. She had been examined four months prior to the injury, and her physician had found the breasts to be normal.

In the Supreme Court ruling "appellants point to the circumstance that six physicians testified that there was no causal connection, while but one physician expressed the contrary view." The one physician who testified for the plaintiff expressed the opinion "that cancer could develop from trauma sustained in the fall."

Counsel for the store contended that no causal connection had been established between the trauma and the cancer which developed, but the court said: "The point raised by appellants is not new. It arises because of the difference in the medical and legal approach to the question of causation. In the case before us it seems that appellants refuse to recognize that legal determination for responsibility may differ from medical findings as to the cause or source of a disease." The court then cited an opinion of the Supreme Court of Arizona in which it was said: "The difference in the medical and legal concept of cause results from the obvious differences in the basic problems and exigencies of the two professions in relation to causation. By reason of his training, the doctor is thinking in terms of a single, precise cause for a particular condition. The law, however, endeavors to reach an inference of reasonable medical certainty, from a given event or sequence of events, and recognizes more than one cause for a particular injurious result."

The court further stated that ". . . inferences, if rational and natural, which follow from a sequence of proved events, may be sufficient to establish causal connection without any supporting medical testimony." There was, therefore, sufficient evidence of causation to raise a question for the jury; but the counsel for the store contended that, since the doctor who testified for the woman stated only the opinion that the cancer *could* have been caused by the trauma, the opinion was uncertain and speculative, and thus insufficient to support the verdict.

The court, in concluding in favor of the plaintiff, stated: "The record fairly establishes that a question of fact as to causation was presented, which question was properly submitted to the jury." The Supreme Court had ruled in an earlier case, cited in the opinion, that "where there is . . . a difference of opinion . . . the causal relationship between the accident and the disease . . . becomes one for the jury's determination."

Daly v. Bergstedt 126 NW 2d 242
MINN, January 31, 1964
*See Editors Soliloquy -- Page 813.

Justice

Wrong none by doing injuries or omitting the benefits that are your duty.
—Benjamin Franklin

The Chronic Regressed Schizophrenic*

Prolonged Oral Treatment with Carphenazine

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The two general classes of schizophrenic patients recognized by Sainz[1] are: the hyperdynamic, who exhibit psychomotor overactivity, dereistic thinking, hallucinations, delusions and agitation; and the hypodynamic, characterized by withdrawal, apathy, psychic inertia, seclusiveness, bizarre posturing, hallucinations and delusions, blocking of speech, and muteness. Of these, the hypodynamic, chronically regressed type forms the majority of the population in state mental institutions, and always has presented a nearly insoluble therapeutic problem.

It is difficult to determine accurately the severity of the schizophrenic process. Therefore the degree of chronicity, which probably reflects the extent of deterioration, generally has been estimated by the length of institutionalization. Under the conventional management of earlier years, improvement might have been expected in 15 to 20 per cent of patients hospitalized for more than one and less than three years, in about 5 per cent of those institutionalized three to five years, and in only 1 per cent of those requiring hospitalization for more than five years.

On availability of the psychopharmacologic agents the outlook for the chronic schizophrenic patient brightened. Various reports have indicated that psychotropic medication may achieve some reduction of symptoms in about 30 per cent of patients hospitalized two to five years, and in, at most, 10 per cent of those who have required hospital care for more than five years.

No single psychoactive compound has proved suitable for all types of mental disturbances; furthermore, no medication of any kind may be expected to lessen symptoms suddenly or dramatically in a long-term, firmly established mental derangement, such as chronic schizophrenia. An intensified research program was organized, therefore, to develop an agent that combined maximum effectiveness for the regressed, hypodynamic patient with sufficient safety for long-term use.

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The piperazinyl compounds appeared to promise greater antipsychotic activity with less risk of toxicity and fewer serious side effects than had been afforded by earlier psychotropic derivatives of the phenothiazine series. Extrapyramidal disturbances developed in some cases, severe enough to threaten the usefulness of such agents. However, one of these substances, carphenazine proved encouraging in preliminary studies. Extended pharmacological trials[2,3] suggested considerable latitude in dosage, flexibility of schedule, and a wider difference between the optimal therapeutic dose and that productive of dystonic symptoms.[4] The average effective dose seems to lie between 100 and 150 mg. per day. As much as 800 mg. daily has been safely administered.[5]

Various publications on the compound[4-7] led to a clinical investigation of carphenazine for hypodynamic, chronically regressed schizophrenic patients at this hospital. The entire range of treatment had been employed for the majority, including electrotonic, insulin and atropine coma, and a variety of established and experimental ataractic compounds, antidepressants, sedatives, anticonvulsants and antiparkinson agents. Little if any alteration of symptoms had been achieved and no approach to "social remission." The reported findings in two controlled studies[6,7] totaling 101 patients were used as a basis for comparison.

Material and Method

Thirty-one hypodynamic patients who had retrogressed steadily toward total deterioration were admitted to the study. They ranged in age from 18 to 64, with an average of 45. Eight (26 per cent) were men; 74 per cent were women.

Diagnoses are indicated in the table:

TABLE I

Schizophrenic Reaction	
Paranoid	11
Hebephrenic	5
Catatonic	2
Schizo-affective	3
Undifferentiated	4
Post-partum	1
Sociopathic personality with sex deviation	1
TOTAL	27

The patients had been hospitalized for an average of eighteen years.

Treatment Given

Carphenazine was administered orally, usually in an initial daily dose of 25 to 150 mg. The starting dose was increased, if indicated, in increments of 50 mg., generally at intervals of seven to ten days. No patient received more than 200 mg. per day. The dose was decreased in two patients to control side effects. An antiparkinson agent, which had been used previously, was continued for one. For a patient with long-standing, paranoid involutional psychosis, chlorpromazine was continued, in a daily dose of 75 mg., a smaller amount than that previously used.

Routine pretreatment laboratory studies revealed no significant aberrations.

Hemoglobin was determined for 24 patients before start of medication; the findings were within the range of normal for 15 and slightly low (11.4 to 12.9 gm.) for nine. Leukocyte counts were done for the same 24 patients; the findings were within the normal range for 22, and slightly elevated for two (11,200 and 12,800). The blood cholesterol was determined for one and the blood sugar for another; both were normal. Urinalysis, done for 25, showed negative results for 24; one specimen was cloudy and opaque (this patient had a slightly elevated white blood cell count). An electroencephalogram was taken for the patient whose schizophrenic reaction developed post partum; the tracing was normal.

Results

Results of treatment are shown in Table 2. The patients were graded according to the methods used by previous observers.[6,7] A favorable response (slight to pronounced improvement) was obtained in 75 per cent (23 patients). Thus the percentage of improved patients fell within the range reported in the two previous controlled studies.[6,7] Seven patients have been discharged provisionally, including one who had had a lobotomy but who obtained a remarkable modification of the schizophrenic symptoms during one year and eight months (613 days) of medication (Case 1). This patient and one other are continuing the treatment as outpatients. Twenty-four are still in the hospital, including the other lobotomized subject, who improved moderately under three hundred eighty-three days of carphenazine therapy. Twenty of this group are still undergoing treatment.

The patient with a post-partum schizophrenic reaction showed improvement for the first time after six months of medication. Although still quiet and preoccupied, and still showing a slight dysphonia, she now functions well.

There was no correlation between the degree of improvement obtained and the length of the episode under treatment or the total duration of illness. However, the duration of carphenazine therapy appeared to exert a significant influence on the clinical response. The patients who showed most pronounced improvement were treated for an average of one and one-half years or more; those in whom no change was detectable, for only three and one-half months (Table 2). These findings tend to agree with those reported previously by others.

Side effects developed in four patients (13 per cent). Akathisia occurred in three, which was controlled in one by reduction of the dose, and in two by discontinuance of the medication. One patient became drowsy; somnolence subsided, however, when the dose was reduced.

Case Report

In 1949 a 24-year-old woman was committed to a state hospital after a suicide attempt. She received electrotonic therapy and later in the year was discharged to her home, where she did not adjust well and had auditory hallucinations to which she responded. Two years after her first admission she was readmitted, exhibiting depression, definite deterioration, destructiveness, and insistence on remaining in bed. She received 99 insulin shocks and 13 electrotonic treatments, as well as psychotherapy, and two years later was transferred to another hospital. Physical and laboratory examinations yielded essentially normal findings. She was withdrawn but oriented, was depressed, anorexic, and delusional. The diagnosis was paranoid schizophrenia.

One year after her second admission, electrical intracerebral stimulation produced transitory improvement. One month after this treatment she had a prefrontal lobotomy, then was treated with chlorpromazine, and one year later, with a series of 21 electrotonic treatments. Her delusions having persisted during three years in this hospital she was not considered significantly improved. Treatment with trifluoperazine was later substituted for medication with thiopropazate and methylphenidate, and reserpine; and she improved somewhat.

Her condition was re-evaluated in 1961. She was still withdrawn and had delusions but usually was co-operative. In March, 1961 medication with carphenazine was started, in a daily dose of 150 mg. She began to improve, became less withdrawn and more cheerful, took an interest in her appearance, and ceased to talk about her delusions. In this condition, and on the same dose of carphenazine, she was provisionally discharged to a sister, with instructions to return to the outpatient clinic at intervals.

Four Weeks Later

The patient looked neat and attractive but showed blunting of affect, as in previous years. She had been helping with the housework and had participated in outside activities. She described somewhat unpleasant dreams but showed little evidence of delusions. The dose of 150 mg. carphenazine was maintained.

Five Weeks Later

The patient continued to look and do well and had gained weight. Her delusions seemed to have receded and she showed no tendency to stay in bed. The dose was not changed.

Seven Weeks Later

The patient had continued to improve, was doing

TABLE 2

Response of 31 Hospitalized Mental Patients Treated with Carphenazine

	Improvement					
	Pronounced		Slight to Moderate		No Change	
	no.	%	no.	%	no.	%
	3	10	20	65	8	25
	Duration of Treatment					
Range, days	487-613		48-622		18-237	
Average, days	569		310		106	
	(1½ years.+)		(10 mos.+)		(3½ mos.)	

most of the housework, cleaning and laundry, was getting along well with her family, and had visited a relative in another city. Her delusions continued to recede. The medication was reduced to 100 mg. per day.

Nine Weeks Later

The patient had relapsed; she was depressed and her delusions had recurred. Her relations with her family had deteriorated; she lacked self-control, was critical and inactive, and laughed meaninglessly. The dose was increased to 200 mg. per day.

Six Weeks Later

The patient showed much improvement, was only mildly depressed, and her delusions were subsiding. During this period her mother had been committed to another state hospital; and the sister with whom she lived had had an acute depression and had entered a private psychiatric hospital. The family felt that the patient's relapse contributed to the sister's breakdown. During the sister's hospitalization the patient assumed more household responsibilities and did the shopping. The 200 mg. dose was continued.

Two Weeks Later

The patient continued to do well but reported occasional episodes of what had been considered diffuse anxiety. Examination showed a little cogwheel rigidity, from excessive medication. The daily dose was reduced to 150 mg.

Seven Weeks Later

The patient had entered her parents' home, seemed to be doing well, was not depressed, mentioned no delusions, did housework, helped with the cooking, and did the shopping. The dose of 150 mg. was continued.

Twelve Weeks Later

The patient was still living with her parents, where she was much needed. She had full charge of the household, since her mother, who had been provisionally released, was unable to assume home duties. The patient looked well, was neat and well groomed, and expressed no delusions.

Six Weeks Later

The findings in physical examination were unremarkable; there were no clinical signs of parkinsonism. In summary, this paranoid-schizophrenic, young adult woman, in nine years of conventional psychiatric treatment, showed no significant or lasting improvement until the final six months, during which she received carphenazine, 150 mg. per day. After provisional release to her family she was seen for fourteen months, at intervals of one to three months, in the outpatient clinic. She relapsed briefly when the daily dose was reduced to 100 mg. but recovered her former gains when the 150 mg. dose was restored. She was then considered ready for full discharge; meanwhile she continues to function well in her parents' home, under daily medication with 150 mg. carphenazine.

Summary

Thirty-one hypodynamic, chronically regressed schizophrenic patients who had been hospitalized an average of eighteen years were treated orally with carphenazine. The initial daily dose of 25 to 150 mg. was increased or decreased as desirable, the maximum daily dose being 200 mg. Twenty-six patients exhibited various types of schizophrenic reaction; a variety of psychoses were diagnosed in four; and one was a sexual deviate with sociopathic personality. Medication was continued from eighteen to six hundred twenty-two days.

The clinical evaluation showed a favorable response within the range of 60 to 89 per cent. The most satisfactory improvement occurred in patients who were treated for one and one-half years or more.

Side effects developed in four (13 per cent). Drowsiness and akathisia (in one patient each) were controlled by reducing the dose. Akathisia in two others necessitated discontinuance of the treatment.

Carphenazine appears suitable for long-term antipsychotic medication of hypodynamic, chronically regressed schizophrenic patients. To obtain significant mitigation of symptoms, therapy should be continued for considerably longer than the three-month period heretofore recommended.

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A glutton digs his grave with his teeth.—French proverb

Experience with 40 Cases of Ectopic Rhythms Using the Direct-Current Cardioverter

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THE USE of an electrical discharge across the chest to correct cardiac arrhythmias dates back to Prevost and Batelli[1] who reported their work in Europe in 1899. It was not until 1932 that Kouwenhoven[2] demonstrated the effect of alternating current on ventricular fibrillation. Zoll[3] and colleagues of Boston, in the late 1950s demonstrated the use of countershock for the treatment of ventricular fibrillation and also atrial arrhythmias. Lown[4] of Boston has made a most important contribution by introducing a synchronized direct current defibrillator or "cardioverter." After using both alternating current and direct current we have no doubt that programmed direct-current shock, i.e., the Lown cardioverter, is superior for both the open and closed chest cardioversion, and have adopted the use of the direct-current defibrillator for correcting all forms of cardiac arrhythmias encountered in heart surgery. Since the adoption of the induced ventricular fibrillation technique to arrest the heart in repairing specific intracardiac lesions, such as interatrial septal defect, it has become mandatory that a most efficient and harmless technique of defibrillation be available. The direct-current cardioverter has repeatedly proven itself to be most satisfactory for this purpose.

The concept of direct current depolarization is best presented by considering the difference between the AC and DC techniques; the following chart summarizes this. The values presented are the doses of electricity used for closed-chest heart "depolarization":

This work was supported by the United Fund of St. Paul, The Hill Family Foundation, and the I. A. O'Shaughnessy Foundation.

The authors are grateful to Edward C. Berger and Sister Victorine Long for their technical assistance.

A) Alternating-Current Technique:
110 Volts
.2 second
12 cycles — 60 cycles per second, or
12 cycles per .2 seconds
B) Direct-Current Technique:
2500 — 10,000 Volts
.002 seconds
½ cycle — a direct current pulse

It must be emphasized that the extremely short duration (.002 seconds) of the current pulse applied to the heart allows exact programming of the shock at any chosen point in the cardiac cycle. It has been established by cardiac physiologists that the optimal point for successfully "depolarizing" the heart without danger of ventricular fibrillation is near the peak of the R wave; therefore we have used this instant in the electrocardiogram cycle to apply the shock.

Technique

Since the technique proved so valuable in the operating room and as an emergency procedure, it was felt justifiable to try it on an elective basis as suggested by Lown. In January of 1963 we were given the opportunity to treat a drug-resistant atrial fibrillation with the cardioverter. Since this was our first elective clinical case we used all safety measures possible. The patient was previously anticoagulated with warfarin. General anesthesia with a muscle relaxant and intratracheal intubation were employed. The number of separate shocks varied from one single shock to eight shocks. The position of the paddles on the chest corresponded to chest leads V_1 and V^6.

We have also tried anteroposterior paddle placement and are not yet prepared to say which method is superior. The anteroposterior technique is slightly more difficult with the patient under general anesthesia.

As experience has been gained, the technique has become more simplified. At present a very light anesthesia of pentothal is employed without endotracheal intubation and without muscle relaxants. Anticoagulants are no longer used unless there is a history of embolic phenomena or evidence of mitral valvular disease. In patients not suspected of drug sensitivity it seems advisable to begin a maintenance dose of quinidine prior to cardioversion.

Results

The following summarizes our experience over a twelve-month period:

Arrhythmias	Failures
34 atrial fibrillation	4
2 atrial flutter	0
4 ventricular tachycardia	0
—	—
40	4

Our first patient converted to sinus rhythm with the second shock of 150 watt-seconds, equivalent to approximately 4000 volts. Unfortunately this patient could not tolerate any drug available for prophylaxis and reverted to atrial fibrillation after ten months.

Of the 34 cases of atrial fibrillation, 12 were patients who had had previous mitral surgery; two of these could not be converted to sinus rhythm. There were two other failures. Two patients with atrial fibrillation who did not convert to sinus rhythm on the first trial were converted on a second attempt.

Failure to Convert

One patient could not be converted to sinus rhythm on several attempts. Since there is little doubt that the myocardium was "depolarized" by the current applied to the chest, failure to convert the arrhythmia was most likely due to the normal sinus mechanism not being available to take over as pacemaker in the short period of arrest before the abnormal rhythm resumed. The voltage required for cardioversion varied from approximately 1300 volts (50 watt-seconds) to 10,000 volts (400 watt-seconds). Two patients have been cardioverted without anesthesia or premedication, both of them with 50 watt-seconds (approximately 1300 volts). Both patients stated there was an instantaneous bolt of electricity across the chest which hurt momentarily; neither however, would prefer general anesthesia; neither would fear to repeat the performance.

Euphoria

A definite euphoria has been noted in all cases of cardioversion. Whether or not this is related to the increased cardiac output is difficult to determine. We are hopeful that a simple method of cardiac output measurement can be developed so that this parameter can be studied.

Reversion to Arrythmia

Unfortunately a long-term follow-up of cardioverted patients is not available at this time. There have been three deaths subsequent to cardioversion — the deaths in no way related to the cardioversion. There is no clinical evidence of untoward effect of the procedure, myocardial damage, or prolonged standstill in any of the cases so far treated; but further experience is needed to fully evaluate the effect of the shock on the severely diseased myocardium. Unfortunately approximately 50-60% of patients have reverted to their original arrhythmia, which points up the fact that drug control is as necessary now as in the days before electronic conversion.

Summary

Since we have now performed cardioversion in 40 cases without any emergency requiring surgical therapy, it is only logical that the elective use of the cardioverter should be primarily in the hands of the cardiologist. Undoubtedly many physicians will feel more secure in the use of such a precise electronic device, which will convert an arrhythmia at a selected predetermined time while under observation and with all ancillary hospital services available, than in a method which terminates the arrhythmia at some unknown moment under the influence of one or more cardio-depressant drugs.

We have successfully cardioverted 36 out of 40 cardiac arrhythmias without untoward incident, two of them without general anesthesia. In selected cases cardioversion would appear to be the method of choice for terminating cardiac arrhythmias, either as an emergency or as an elective procedure.

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Galen's Materia Medica*

For Falling Hair

To prevent hair from falling out, take many bees and burn them and mix with oil and use them as ointment.

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*Thorndike, Lynn – see Minn Med Oct. '63.

Take Time Every Day

Take Time TO LOVE and BE LOVED — It is a God-given privilege.

Les Hopitaux De Paris

Like temples of worship, general hospitals became integral components of large cities centuries ago. The greatest progress was made when people dedicated themselves to assisting others.[6] Hospitals reflect the moral level of any society, and achievements in the arts were accompanied by advances in the art of healing. Wars brought improvements in the technique of surgical therapy, but postwar reconstruction accelerated medical development to an even greater degree. It is likely that patients who submitted to the healing arts of the Greek Temples fared better than the miserable victims of many hospitals 2,000 years later. Only with the conceptual development of antisepsis and asepsis in the hands of Semmelweis, Lister and V. Bergman did the treatment of the ill improve.[5]

At the time of the French Revolution some political and social philosophers attempted to transfer problems of medical financial assistance to government control. The philosophy of individual charity and generosity was declining and the right of the helpless to assistance was regarded as the public duty of society. Ignored was the dictum of the legendary Fabiola who founded the first Christian hospital in 330 A.D., and who maintained that the individual citizen must assume the responsibility of being his brother's keeper. The attitude prevailed, however, that the government owed a responsibility to the citizen.

Despite many attempts to abolish it, L'Hotel Dieu of Paris has become the prototype of a general hospital, not only for France but for the rest of the world as well.[1] It was involved in struggles between the Parisian community on the one hand and the hospital administration on the other. Founded by Clovis II in the first half of the Seventh Century and reconstructed in 1725 under the direction of Michelle Michelon, it is the second oldest hospital functioning "in continuo" in its original location. Connected with the Church of St. Christopher, it was located on the bank of the Seine River close to the Cathedral of Notre Dame. A group of women serving at St. Christopher's Church were ordered by Pope Innocent IV into a regulated society of nuns required to follow the rules of St. Augustus. Thus became established the oldest nursing group, singularly dedicated to their profession.

L'Hotel Dieu is surpassed in age only by the Spiritu Sancti Hospital in Rome.[2] Saint Bartholomew's Hospital in London is the third oldest extant hospital.[3,4]

Due to lack of finances, personnel, and the general low level of nursing, L'Hotel Dieu could not accomplish all the tasks it wished to; nevertheless it did, under most adverse circumstances, maintain its everyday strenuous activities and perform its daily humanitarian tasks. Service to the community, service to the profession, service to science, an example of centuries past for centuries to come, a domicile of medical giants who contributed — this was L'Hotel Dieu.

In 1788, Tenon,[7] a professor of pathology at the surgical college, member of the Academy of Sciences, and a distinguished citizen of Paris, published a treatise on the hospitals of Paris which included plans and detailed statistics, a book which remains a classic on the subject of hospitals. On his commission he had such luminaries as Lavoisier, La Place, and

Continued on Page 892

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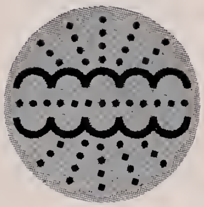

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Editorials

Missed Abortion

ELSEWHERE IN this issue is reported a case of missed abortion (Page 787). When faced with the enigma of this obstetrical catastrophe, most obstetricians inwardly shudder upon contemplating the intervening weeks until termination of the pregnancy occurs, either by spontaneous or operative means. As the obstetrician contemplates the problems which both he and the patient must face together, his contemplation is frequently shattered by a telephone call from the patient's mother inquiring about the danger to her daughter, or as mothers so aptly put it, "carrying a dead fetus around inside the womb." In the past several years with a demonstration of fibrinogenopenia, or as it is called by some authors, afibrinogenemia, we can no longer assure either the patient or the harried relative, that time and nature will alleviate the situation. Contrariwise, we must set a definite time that definitive procedures will be instituted which will result in the emptying of the uterus in the event that nature does not supervene. When do we decide that the uterus must be emptied? It has been fairly well demonstrated that the incidence of fibrinogen deficiency increases with the duration of retention of the no longer viable products of conception. Fibrinogen deficiency occurring less than five weeks after fetal death is relatively uncommon, in fact in one study by Kinch[1] it was found to occur in less than one per cent of unselected intrauterine deaths. We therefore feel that should retention of the products of conception continue beyond three weeks after confirming the diagnosis of intrauterine death, weekly determinations of fibrinogen level should be made. A decrease in plasma fibrinogen level to 100 mgm. per 100 ml. plasma or less indicates an impending coagulation disorder necessitating immediate evacuation of the uterus.

When it comes to consideration of the actual technical procedure of evacuating the uterus we are faced with the time honored methods of (1) dilatation and curettage, (2) abdominal hysterotomy or (3) vaginal hysterotomy. Any or all of these procedures may be extremely traumatic and are frequently accompanied by the loss of rather alarming amounts of blood. Those of us who have managed missed abortion by the use of intravenous oxytoxin, frequently find to our alarm and amazement, that huge amounts of intravenous oxytoxics have to be administered in attempting to institute uterine contractions of an intensity sufficient to result in emptying the uterus. The use of the various medications designed to relax the cervix has re-

Continued

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sulted in little if any improvement in the situation.

Recently Bengtsson[2] described the technique of intra-amniotic injection of hypertonic sodium chloride solution, a procedure which has been found to be extremely effective in the management of missed abortion. I personally have used this technique in five patients. Labor supervened in all within six to eight hours after the withdrawal of amniotic fluid and replacement by hyperonic saline. In one additional patient a diagnosis of intrauterine death was made which was subsequently proven to be erroneous. Two hundred cc. of hypertonic saline were injected into the amniotic cavity at twenty-six weeks gestation. This did not result in an onset of a labor pattern, and the patient spontaneously delivered a normal male infant approximately thirteen weeks later.

As one contemplates further on the problems of abortion, it seems that we are now seeing a higher incidence of missed abortion than existed previously. As one conjectures on the etiologic factors contributing to this seeming increase, we speculate first regarding increased radiation due to fallout and various other sources, second the employment of various medications designed to tranquilize the nervous system, and third the marked increase in the use of synthetic progestins currently on the market. How frequently do we see a patient complaining of a small amount of spotting at five to six weeks gestation who was subsequently started on large doses of the various progestational steroids. Many of these threatened abortions, which in the normal progression would continue to spontaneous abortion, are converted to missed abortion by the extreme potency of the medications used. It must be borne in mind that these drugs are ineffective except in the patient with a true progestational deficiency. In the usual practice we are not making use of the tests necessary to confirm the diagnosis of progesterone deficiency. A plea is made at this time to be much more selective in the type of patient to be treated, thereby decreasing the amount of progestational steroids used in the treatment of threatened abortion. If in this way we are able to prevent even a small number of these gestational aberrancies we will thereby alleviate one of the most harrowing emotional experiences which can occur to the obstetrical patient.

Richard L. Jackson, M.D.
Minneapolis, Minnesota

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1. Kinch, R. A. H.: Canad Med Ass J 85:932, 1961.
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The Paraplegic Patient*

THE CARE of the paraplegic patient becomes the responsibility of the family physician, who may not have had experience in dealing with patients of this type and who may encounter some difficulties in handling the special problems peculiar to them.

If the patients have been adequately rehabilitated and are reasonably motivated to take care of themselves, they get along very well without much medical care. Their most frequent problems relate to infections of the urinary tract and to the ever-present danger of decubiti. The author Schoening* mentions the possibility of ureterovesicle reflux as a cause of pyelonephritis; but one must always be alert to the development of usual urinary tract infections as well as to the possibility of lithiasis.

Decubiti can be prevented, if the patient will maintain a high level of physical fitness, avoiding prolonged sitting, etc.; and he should walk a moderate amount each day. The physician, moreover, may need to give some advice regarding the use of crutches and braces. Al-

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*Schcening, H. A.: Minnesota Med 47:531, 1964.

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so, it may become necessary for the patient to return to a treatment center for a "postgraduate" type of program to ensure continued self-care and independent walking.

The author* discusses problems associated with loss of sensation, particularly those relating to the possibility of intra-abdominal disease. Also it is surprising how many of these patients forget that the affected extremities can be burned or otherwise injured without warning.

Finally, the family physician may be called upon to advise on problems of marriage, or even divorce. Although information is incomplete, several studies indicate that paraplegics encounter special and difficult problems of marital adjustment and consequently have a relatively high rate of divorce.

Donald J. Erickson, M.D.
Mayo Clinic
Rochester, Minnesota

The Air We Breathe

SINCE THE days of the Industrial Revolution, the air of cities has been polluted by chemical waste from the factories in them. Atmospheric conditions and abnormalities from time to time have accentuated the problems that exist in such areas and in some instances have had widespread and fatal results. In 1930 in the Meuse Valley in Belgium, a dense fog and a temperature inversion prevented the usual upward escape of air pollutants from local heavy industry, resulting in irritation of the nose and throat with cough and dyspnea. Sixty deaths occurred in elderly people with chronic cardiopulmonary disease. Sulfur dioxide and sulfuric acid were the chief suspects, although the specific agent was never identified.

In 1952 and again in 1956, London experienced heavy fog associated with an unusually high frequency of respiratory illness and mortality that began a day or so after the onset of these adverse conditions. As in Belgium, the most seriously affected groups were the elderly; infants, too, were overcome by the atmospheric poisons. In 1954, the town of Donora in Pennsylvania had a similar environmental disturbance due to temperature inversion, and oxides of sulfur were again blamed for the high mortality rate in infants and the elderly. Attacks of asthma have troubled residents of Yokohama and New Orleans and also have been attributed to atmospheric pollutants. Although allergic factors have been considered in the etiology, there is accumulating evidence that prolonged and repeated exposure may result in permanent impairment of pulmonary function. In the Los Angeles area, smog has become a major problem. Smog is due to the peculiar climatic conditions that exist along the coast of California, together with the photochemical disturbances that occur in atmospheric impurities from the exhausts of innumerable automobiles. Carcinogenic hydrocarbons have been found in the ambient air of various cities of the world as have oxides of sulfur and nitrogen, carbon monoxide, and metallic particles of various kinds.

Of all the internal organs of the body, the only one in direct communication with the environmental atmosphere is the lung. The lung is entirely exposed to the air that we breathe and to all the dusts and fumes that it contains. Respiratory infections of trivial or severe degree result from inhalation of infecting organisms. Occupational exposure to air pollution may cause acute poisoning or more chronic and specific diseases of the pneumoconiosis group. The air of the industrialized cities of the world has been shown to be sufficiently contaminated so as to affect adversely the health of their inhabitants. Pulmonary emphysema is a more frequent cause of death in metropolitan areas than in rural ones and is influenced adversely by polluted atmosphere.

Although it has been generally acknowledged that cigarette smoking is a major

Continued

In systole and diastole, the human heart produces a maximum signal of only a few millivolts between two ECG limb electrodes. Mixed in with this tiny signal may be some unwanted electrical "noise", caused by power lines, nearby X-ray or diathermy machines, or even ordinary office equipment. Until now, eliminating this noise from the record usually meant time-consuming adjustments and rerunning records until the complexes were clear.

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cause of cancer of the lung, there is no doubt that other factors have an important part. Studies in Europe and in this country have led to the conclusion that a difference in cigarette smoking alone is not responsible for the excess of lung cancer in city dwellers. It has been shown that emigrants from Great Britain to New Zealand and South Africa have a higher incidence of lung cancer than have native born residents and that this is not related to their smoking habits. Prior exposure to polluted air in the cities of Great Britain has been suggested as significant in the genesis of lung cancer in these emigrants.

In the not too distant past, the ravages of contagious diseases and their spread through the medium of water and food were major problems that the hygienist was able to overcome. Contamination of water and food has been replaced by pollution of the environmental atmosphere as a major public health problem. Advances are now being made in meeting this problem, but much remains to be done.

Although the adverse effects of these pollutants on intact or diseased lung are well recognized, the details of their action are not understood as yet. Identity of individual toxins and details of the defensive response of the lung remain obscure. The continuous movement of the chemicals of the atmosphere and the rapidity of their molecular interchange make accurate sampling of air difficult. Particles less than two microns in diameter are capable of reaching the alveolar spaces, but the mechanism of pulmonary macrophage or other defenses in handling these particles is not known. On the other hand, disabling respiratory disease in city dwellers is becoming increasingly common. In 1964, it is astonishing that we are so complacently ignorant of the many fundamental problems concerning the air that we breathe.

Matthew B. Divertie, M.D.
Mayo Clinic
Rochester, Minn.

Letter to the Editor:

My article "Phenylketonuria in Minnesota" (Minnesota Medicine, May, 1964, p. 502) contains an error relating to the Guthrie test.

The present sentence is as follows: "The growth of the bacillus is inhibited by the presence of phenylalanine."[10]

This sentence should read: The growth of the bacillus is inhibited by the presence of thienylalinine, and phenylalanine reverses the effect of it; and a direct relationship is present between the phenylalanine blood level and the growth of bacillus subtilis.[10]

Robert O. Fisch, M.D.
Minneapolis, Minn.

Deep, Deep Down In The Dumps?

"Deep" is deeper than "profound," and "lonely" is lonelier than "solitary."—W. D. Snively, M.D.—Pagentry of the English Language.

“. . . their feelings of anxiety seemed to contribute to the urge to overindulge in cake, candy, and other rich food.”[1]

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1. Viglione, J.P.: Clin. Med. *69*:1157 (May) 1962.

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The Editor's Soliloquy

The Courts vs. the Etiology of Disease

A recent decision of the Supreme Court of Minnesota* upheld the jury verdict from the district court that carcinoma of the breast was caused by an incident of injury sustained while shopping. The patient was accordingly awarded damages.

Such a decision becomes a terrifying circumstance, for it would seem that when a factual judgment of this nature can be made by a group of laymen who are totally uninformed in the intricacies of medical science, even though this fact cannot be established by qualified medical scientists, the etiology of all disease could soon be established by the legal profession as being due to trauma. With the Supreme Court's proclamation, every individual with carcinoma becomes a potential litigant against some other party, if he can dream up even a remote incident of injury.

Over the years, in the course of examining patients who have suffered incidents of injury in which litigation for possible liability is pending, it has been observed by numerous physicians that some plaintiffs and their attorneys attribute an almost endless variety of symptoms or disease to an incident of injury. The makers of brooms may find themselves being sued for negligence in not having padded the ends of the handles in order to protect housewives from bruising their breasts; property owners may become involved in litigation for possessing attractive nuisances against which trespassers can bark their shins and collect damages for all subsequent aches and pains in the legs; restaurant owners, clubs, churches, bowling alleys, night spots, public transportation systems, all may become potential defendants in suits brought by clumsy plaintiffs who have envisioned an insignificant injury as a factor in subsequent disease: headache, neckache, backache, hemorrhoids, appendicitis, ingrown toenails, warts, brain tumors, falling hair, etc., etc., to say nothing of the damage that may have been inflicted upon family compatibility. If we are to conclude that trauma is a factor in causing all disease, then the medical books must be revised.

Trauma is an entity of its own, and when incurred in any significant amount it is always evident with objective findings early in the course of the illness. Injury has one pattern which is basically constant, just as is the pattern of all disease. Cells are damaged, whether bruised, sprained, strained, torn, ripped, severed, or cut, and there is extravasation of blood (ecchymosis) and exudate of plasma (swelling) which is on the whole evidenced directly in proportion to the extent of the original damage. Immediately thereafter the healing process begins, as the damaged area is infiltrated with plasma cells. Fibroblasts then proliferate and their fibers and tendrils extend and grow across the defect to repair the damage (induration). The cells of muscle, bone, fibrous tissue, mucous membrane, skin, blood vessels, all regenerate, and the extravasated cells and plasma are reabsorbed (softening of the induration). This early healing process covers, in most instances, a period of about ten days. Thereafter the immature cells which have taken part in this healing drama become progressively more developed, and their maturation process may extend over a

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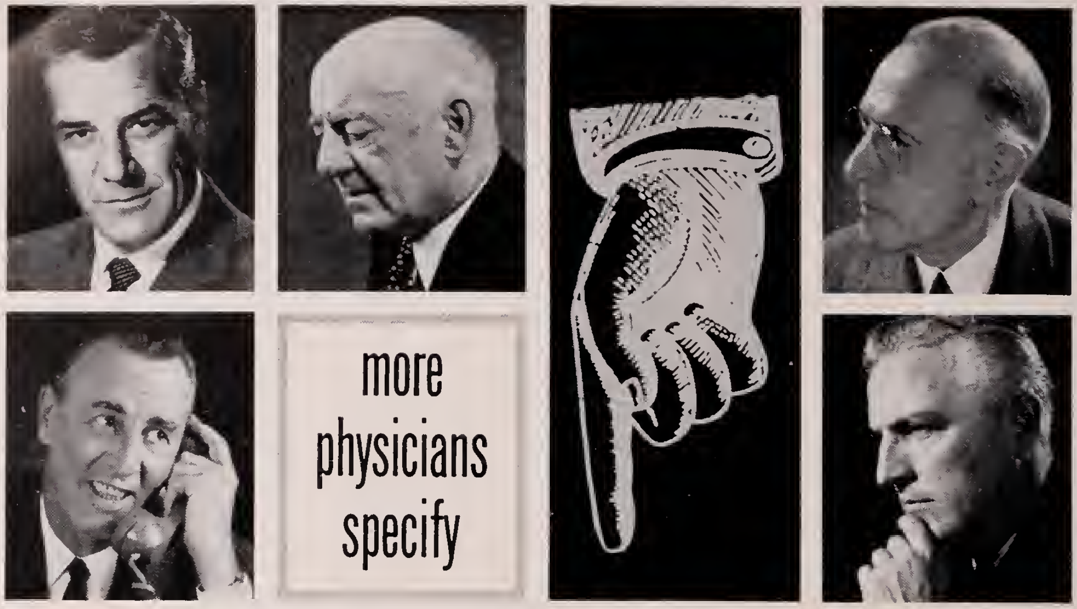
*See It's the Law, Page 794

Continued

Photos posed by professional models



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period of 30 to 90 days, when the tissues again become normal with insignificant scar tissue (no induration). If infection supervenes, the healing period may be extended and the scar tissue more extensive. If the injured tissue has been massively separated, the scar tissue is more extensive; but if the injured tissues have been only bruised, strained, or sprained the healing process leaves insignificant or no scarring.

If another disease process exists in the body, or within the vicinity of the traumatized area, that other disease process remains intact and is inappreciably influenced by the adjacent trauma. A pre-existing disease process, if bruised, may be temporarily aggravated; but when healing is complete, the pre-existing disease remains in its original state, subject to its own physiologic rules and regulations. A carcinoma mass, if bruised directly, could be disseminated but no new disease initiated by the injury; nor can cancer be caused by one incident of trauma.

If the healing period from an injury seems to persist beyond the usual period of regeneration, then the physician should look for other sources of disease. Finding such disease, whether in juxtaposition to the traumatized area or not, will not appreciably alter the healing period of an injury, nor will the coexisting disease itself be significantly altered in its progress, by merely being adjacent.

Fifty years ago it was thought that trauma might be a factor in the development of carcinoma, but the studies of numerous scientists have long since proven that trauma is not such a factor. For the courts to have suddenly decided that carcinoma of the breast could have been caused by an injury delivers the entire gamut of disease etiology into the ponderings of medically uninformed judiciary bodies — because the courts have now so proclaimed. Scientific treatises of the Hindus centuries ago made reference to demons as one of the sources of disease. For the courts to now proclaim trauma as a cause of disease is fully as ridiculous as having faith in incantations as a cure for snakebite. With one fell swoop, the need for scientific etiology has been eliminated. Why bother about further research? It is ludicrous to contemplate!

Carl O. Rice, M.D.

The Emperor's Bellyache

Not only manual dexterity but also shrewd psychology was demonstrated by the ancient physician: Summoned to the Emperor's bedside and desiring not to demean royalty by prescribing the usual plebeian remedy for common stomach-ache, Galen flattered the Emperor by telling him that were he, the Emperor, a common person, "wine sprinkled with pepper" would be prescribed, but that in his special case "warm spikenard ointment enveloped in purple wool" was indicated. The latter was forthwith applied to the royal stomach in Galen's presence; but after his departure — and not until then — did the Emperor call for "wine sprinkled with pepper," which he drank — with the subsequent pronouncement that he had "one physician, and he was a perfect gentleman."

Education makes people easy to lead, but difficult to drive — easy to govern, but impossible to enslave.—J. Morris Jones

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Curbstone Consultation

Phenobarbital

QUESTION: An epileptic child is under my care. I have been controlling her seizures with phenobarbital, 100 mgm. daily in divided doses. Because she is lagging somewhat in her performance in school, the parents are concerned whether this might be a result of the medication she is now receiving. I hesitate to change to another preparation, because she is controlled so well on phenobarbital. Do you think that phenobarbital can be implicated as interfering with this child's intellectual attainment? *M.D., Mankato*

ANSWER: I would recommend that you continue the same program of management you are currently employing, noting that you are highly pleased with the manner in which you have been able to control this child's seizure. It is unlikely that change in medication would improve her attainments in school, and one would have to look elsewhere for an explanation as to her poor showing in her studies. Phenobarbital used in the dosage you have indicated does not appear to interfere with the learning behavior of these children.

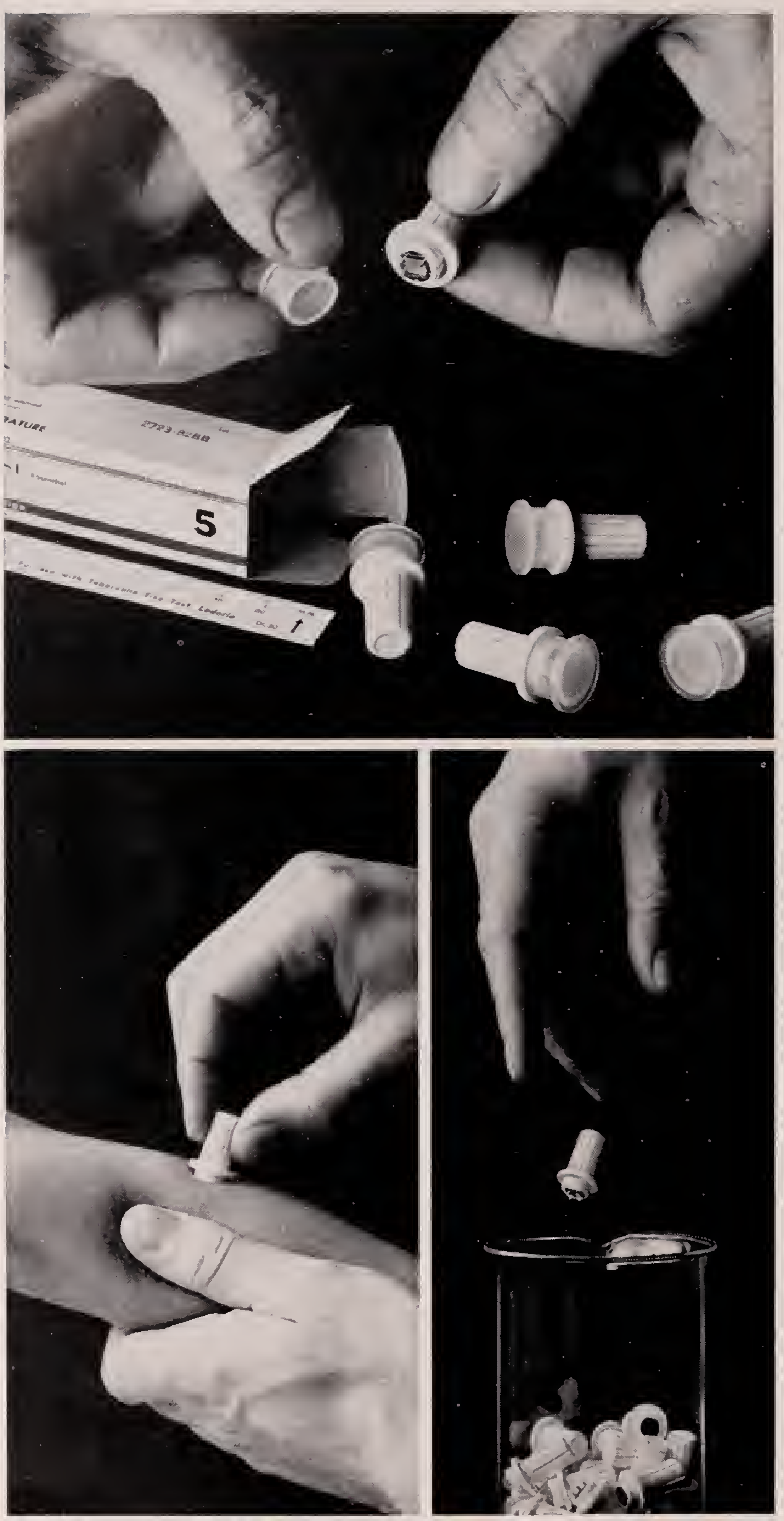
Torsion of the Testicle

QUESTION: I have a 23-year-old patient who suffered a torsion of the left testicle, which became atrophic following conservative management. He is now concerned that he may become sterile if the same thing should happen to the other testicle. Does he have an increased likelihood over a normal individual of developing torsion of the unaffected testicle?

M.D., St. Paul

ANSWER: In the patient described, since surgical intervention was not carried out, one could not say whether the torsion was extravaginal or intravaginal. The latter type, however, through a "bell-clapper" deformity, accounts for over 90 per cent of recorded cases of testicular torsion. Since this deformity, leading to torsion, is a bilateral anomaly in over 50 per cent of cases, if eunuchoidism secondary to contralateral testicular torsion is to be prevented, contralateral orchiopexy should be done. In those cases of testicular torsion treated by immediate orchiopexy the uninvolved side should be treated in a similar fashion at the same time. The reluctance to explore the second testicle for fear of damaging it is unfounded when orchiopexy is correctly carried out.

Life's taxi keeps marking up the nickels, whether you are driving anywhere or just sitting still.—Cominco Magazine



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Complication with Undisplaced Colles' Fracture

The Colles' fracture is an injury seen frequently and one which is often thought of as being uncomplicated in nature and routine in method of treatment. It is often referred to as "a simple fracture," using that connotation to imply simplicity rather than to infer "not compounded." However, there are pitfalls with this fracture as there are with most fractures, and the surgeon must recognize potential complications if he is to avoid them.

Careful follow-up evaluation of all Colles' fractures must be made in the three weeks following reduction. Frequently, there is redisplacement, especially if there has been comminution. Therefore, it is extremely important to have follow-up X rays at least once during the first week and at the end of each week for the first three weeks. If no appreciable shift in alignment has occurred by then, another X ray is not indicated until five to six weeks following fracture, at which time final removal of the plaster is usually anticipated.

Occasionally, a fracture which was initially undisplaced will subsequently shift alignment. A regrettable sequence of events is illustrated in the following case:

A 70-year-old white male was seen in an emergency room on the evening of the day he fell and injured his wrist. X rays were taken and showed an essentially undisplaced Colles' fracture (Figure 1). A long arm cast was applied without the need for anesthesia. Two days later, the patient was seen in the Outpatient Clinic where follow-up X rays were taken. These X rays showed no change in position. Because of the fact that there was no appreciable displacement on the original films, it was felt a short arm cast was sufficient. The existing cast was shortened to below the elbow.

The patient was not asked to return for one month. He was seen one month after the date of his injury, at which time the cast was removed and X rays out of plaster were taken (Figure 2). Obvious displacement of the distal radial fragments had occurred with marked shortening and volar angulation. No good evidence for healing could be identified on those films. Nonetheless, no further cast was applied.

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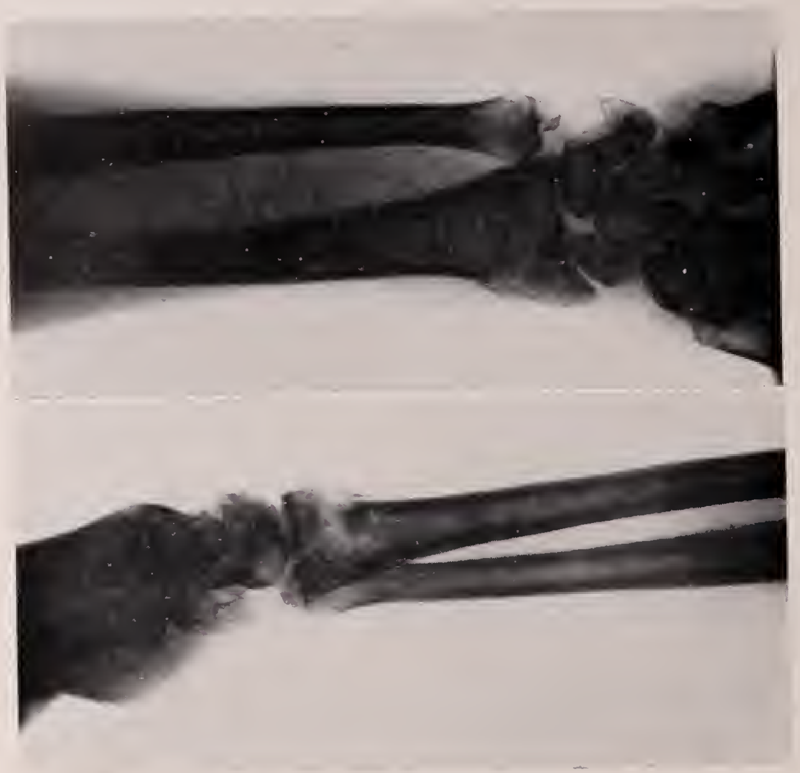

Fig. 1 — Initial X rays.

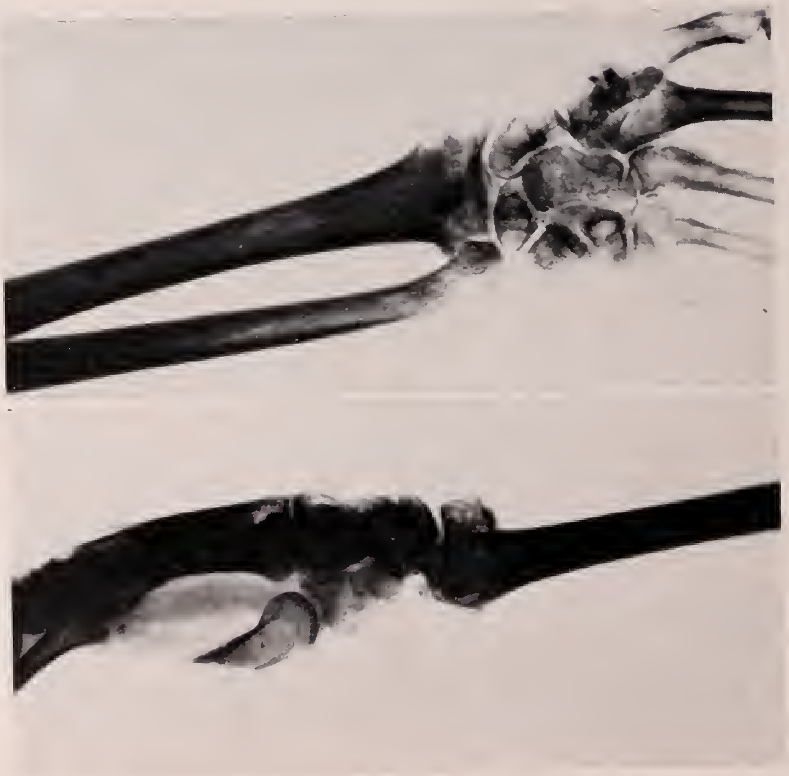

Fig. 2 — X rays taken out of plaster, one month after fracture. Plaster immobilization discontinued at this time.

The patient was not seen again for six weeks, when follow-up X rays revealed further dorsal displacement of the distal radial fragments and still no evidence of union (Figure 3). At this point — ten weeks after fracture — the notation of "non-union" was made in the chart. The patient was experiencing continued pain in the wrist with weakness of the hand and wrist. There was obvious deformity of the wrist (Figure 4). His problem was presented to the Fracture Conference for opinion.

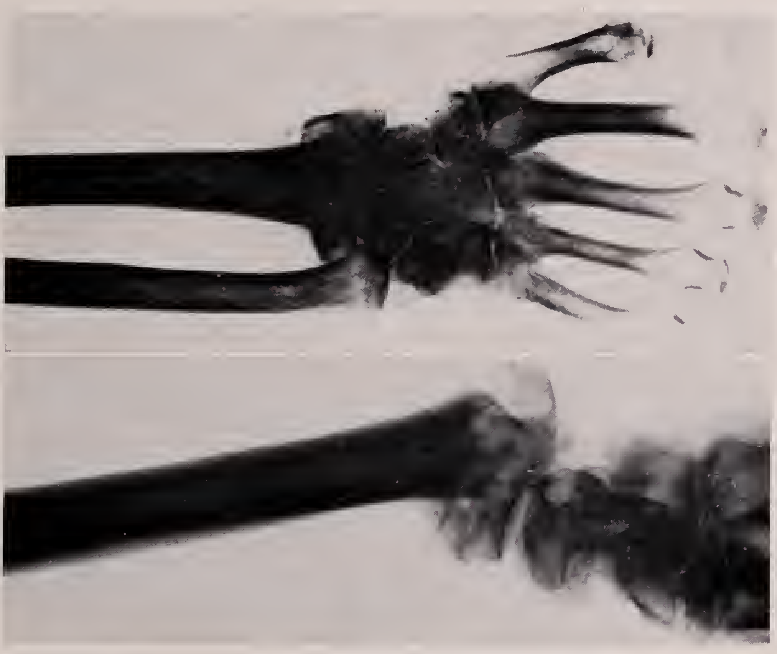

Fig. 3 — X rays taken ten weeks following injury.

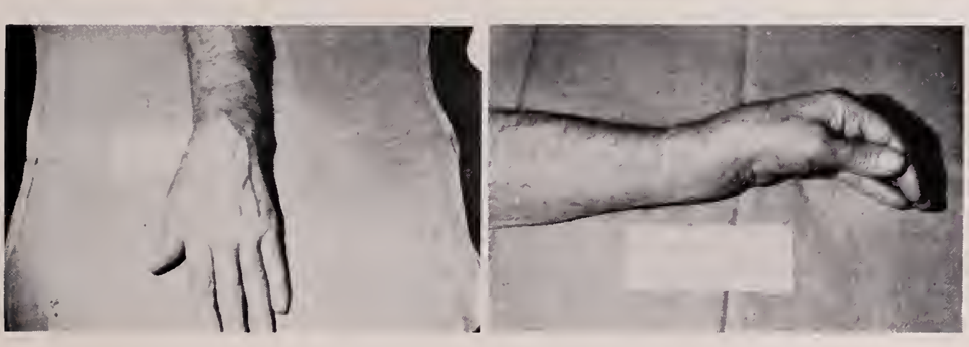

Fig. 4 — The patient's hand and wrist ten weeks following injury.

The advisability of further treatment for this patient's problem arose. Although the function of the hand and wrist was definitely limited because of restricted range of motion and discomfort, a worse situation might be anticipated with remanipulation and further immobilization at this time in a 70-year-old man. Should a true nonunion occur, it might subsequently become necessary to resect the distal ulna and open the radial fracture with

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the intent of internal fixation and bone grafting. Rather than to recommend to this particular patient this amount of additional surgery, it was decided in the Fracture Conference to temporize — to wait and see how he tolerated his existing disability.

Four weeks is usually too soon to remove plaster immobilization in the treatment of a Colles' fracture. Six weeks of immobilization is routine, and sometimes eight weeks is necessary in comminuted fractures. Whether or not a long arm cast is necessary is debatable; its use often depends upon the individual doctor's experiences and the general status of the patient, considering such factors as (1) age of the patient, (2) his ability to help himself with a long arm cast in place, (3) fear of causing stiffness of the elbow and shoulder in older individuals, and (4) the degree of comminution of the fracture itself.

This rather dramatic example of serious complication in the treatment of "a simple Colles' fracture" should teach all of us not to be lured into the false presumption that an undisplaced Colles' fracture will inevitably heal in good alignment with little or no disability. Careful follow-up X-ray evaluation is necessary in all of these fractures with prompt re-reduction if significant shift of fragments occurs.

Frederick E. Drill, M.D.
Minneapolis, Minnesota

Blaming the Stars

"This is the excellent foppery of the world, that when we are sick in fortune, — often the surfeits of our own behaviour, — we make guilty of our disasters the sun, the moon, and the stars: as if we were villains of necessity; fools by heavenly compulsion; knaves, thieves, and treachers,* by spherical predominance; drunkards, liars, and adulterers, by an enforc'd obedience of planetary influence; and all that we are evil in, by a divine thrusting on. An admirable evasion of whoremaster man, to lay his goatish disposition on the charge of a star! My father compounded with my mother under the dragon's tail, and my nativity was under Ursa major; so that it follows, I am rough and lecherous. Fut, I should have been that I am, had the maidenliest star in the firmament twinkled on my bastardizing."

Edmund in King Lear, Shakespeare

*Traitors

Cure Haemophelia by changing the genes. — Today, John Campbell.

One of our national problems is not that of insecticides, but of spiritual homicide.
—Rabbi Heschel at '64 A.M.A. San Francisco Conf.

Tumor Conference

Bronchiolar Carcinoma of the Lung

Bronchiolar carcinoma of the lung is a rare neoplasm, but there have been reports of its increasing incidence in recent years.

Two forms of the disease have been described. Malassez, in 1876, first described the nodular form of this tumor, with the nodules varying from miliary to marble size and the bronchi usually free of tumor. Musser, in 1903, was the first to describe the diffuse form of this type of lung cancer, which resembles a pneumonia in a stage of gray hepatization and may involve a part of a lobe or an entire lung.

Various names have been applied to this disease, because of some difference of opinion as to cell origin. Recently, bronchiolar carcinoma appears to be the term preferred by most pathologists, based on careful review of the histopathology of the cases reported. Some of the other names given are: alveolar-cell carcinoma, pulmonary adenomatosis, malignant adenoma, muco-cell papillary adenocarcinoma, diffuse primary alveolar epithelial carcinoma, multicentric alveolar carcinoma, and diffuse epithelial hyperplasia.

As is true of cancer in general, no single factor can be pin-pointed in its etiology. It is interesting to note that virus etiology has been entertained because of the striking morphological similarity to zaagsiekte in sheep, as reported in a study made by the African Expedition of the Rockefeller Institute for Medical Research, zaagsiekte being a specific catarrhal pneumonia peculiar to sheep in South Africa. It has also been called "drive sickness," as symptoms appear when sheep are driven for long distances. The prevailing view is that zaagsiekte is due to a specific virus.[5]

Case Report

A forty-one-year-old white male schoolteacher was admitted to St. Barnabas Hospital on August 26, 1963, for further evaluation of a persistent large infiltration in his right lower lung field, shown in chest X rays taken in the preceding two months. The last known normal chest X ray of this patient, in December 1957, was taken at the University of Minnesota. In September 1961, he had a chest film (Fig. 1) taken at the Mobile Unit in Minneapolis, which showed a vague area of hazy infiltration over the right second anterior interspace. In November 1961, another chest X ray, taken at the same Mobile Unit, showed no change from the previous finding. He was asymptomatic at that time.

In May 1963, while in Superior, Wisconsin, he became ill with cough and fever and was treated for pneumonia. He did not have chest X rays taken at that time. About a

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month later, while in Tucson, Arizona, he felt ill again with a productive cough, hemoptysis, and fever. He was admitted to the Tucson General Hospital and a chest X ray was taken on June 28, 1963, which showed a large homogeneous density involving the right lower lung field. Treated as a case of lobar pneumonia, his symptoms improved, and he was discharged from the hospital after about a week. However, follow-up film taken two weeks later showed no change in the density in the right lower lung field.

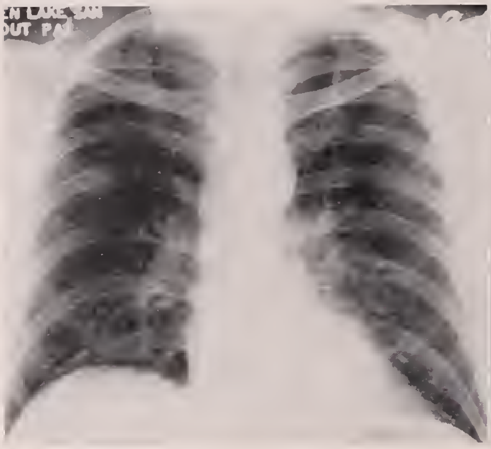

Fig. 1 — Two years pre-operative.

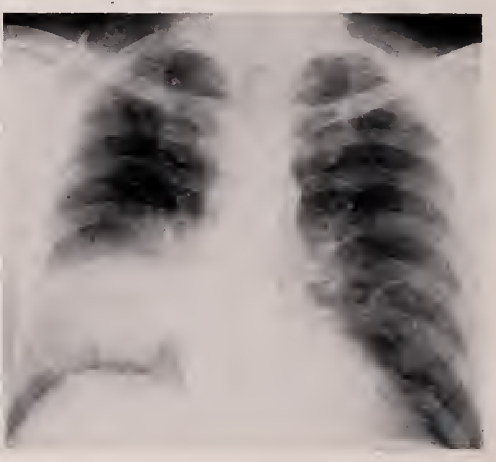

Fig. 2 — Two days pre-operative.

On August 19, 1963, a chest film taken at the Mobile Unit again showed this infiltration, which occupied nearly the entire lower half of the right lung field. Except for a slight cough, the patient was asymptomatic. No history of weight loss was given.

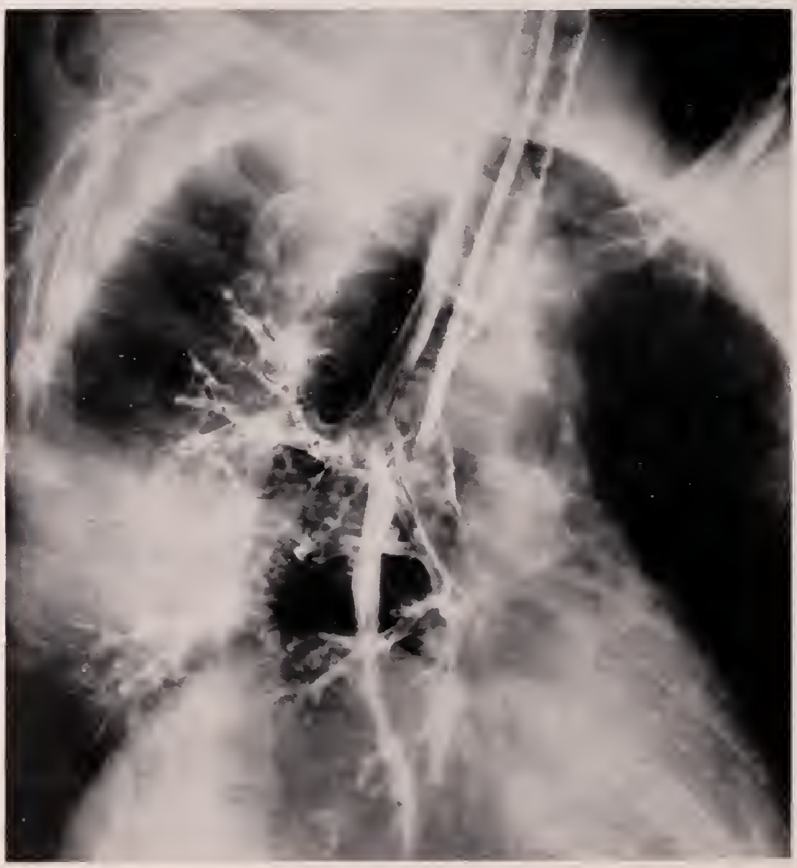

Fig. 3 — Six days pre-operative.

Physical Findings: The patient was well developed and nourished, afebrile, and had no respiratory difficulty. The only pertinent findings were in the chest, where there was dullness on percussion over the right lower lung field. The breath sounds were diminished and coarse rales were present in this area.

Laboratory Findings: Hemoglobin 17.1 gm.%; WBC 9,225/cu.mm., with 54% neutrophils, 27% lymphocytes, 9% monocytes, 8% eosinophils, 1% basophils. Sedimentation rate was 52 mm. in one hour; BSP 4%; alkaline phosphatase 8 King-Armstrong units. Urinalysis was normal. Smear and cultures of washings from right bronchus showed Gram-positive-and-negative diplococci, many alpha strep and neisseria, fewer diphtheroids. No fungus was isolated on cultures after six weeks and no acid-fast bacilli after eight weeks. The Papanicolaou smear of right bronchial washing was negative for malignancy.

Skin Tests: Mantoux 1:1000 and triple fungus (blastomycin, coccidioidin and histoplasmin) were all negative.

Roentgenologic Findings: Chest (8/27/63 and 9/1/63) showed an area of homogeneous density in the superior segment of the right lower lobe consistent with pneumonia. The right diaphragm showed a moderate elevation with possibility of some underlying atelectasis (Fig. 2). A bronchogram (Fig. 3) of the right bronchial tree (8/28/63) showed no definite evidence of endobronchial tumor. The left posterior oblique film revealed an infiltration in the B6 segment extending out to the pleura and probably involving a portion of the posterior basilar segment on the right as well.

Bronchoscopy (8/28/63): This showed bronchitis but all orifices open. No endobronchial tumor was seen.

Right Thoracotomy (9/3/63): The pathologic process was found to involve only the right lower lobe, the upper two thirds of which was solid and discolored. It appeared and felt like liver, and was sharply demarcated from the lower one third of this lobe which appeared grossly normal. A needle biopsy was taken from the diseased portion; a frozen section was done and diagnosed as alveolar-cell carcinoma. A right lower lobectomy was performed. The three peribronchial nodes removed were negative for metastases. Sections taken from the lung specimen showed the multricentric origin of the tumor (Fig. 4).

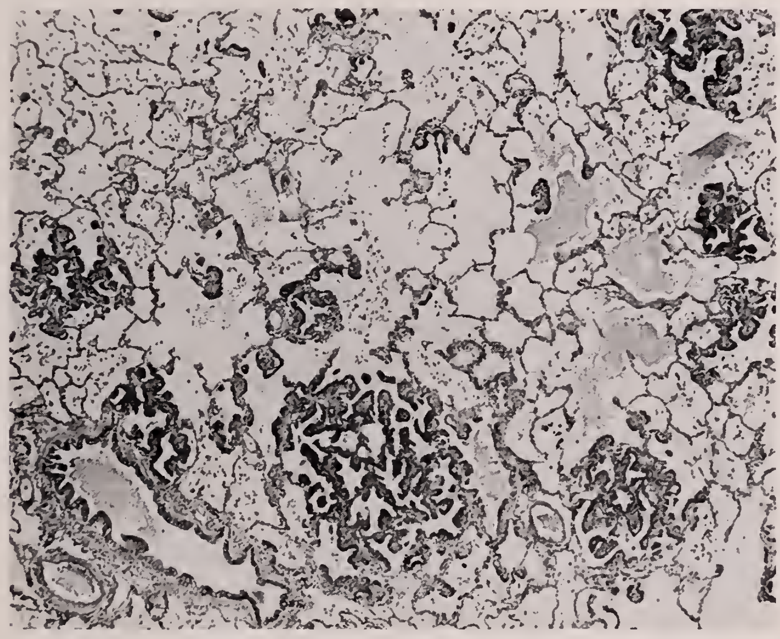

Fig. 4 — Representative field showing the multicentric origin of the tumor.

Clinical Manifestations

Generally, the chief complaint is nonproductive cough which later becomes productive. However, many cases show no pulmonary symptoms. In one series of thirty-three patients, 58% were free of pulmonary symptoms. Other common symptoms are hemoptysis, dyspnea, fatigue, weight loss,

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back pain, pain in the chest, anorexia, orthopnea and night sweats. Fever, although mentioned in some cases, is not a prominent feature. The findings on physical examination are few. There may be dullness, with decreased breath sounds and rales over the affected pulmonary areas. It is not unusual for patients with this disease to exhibit no abnormal physical findings in the thorax.

Incidence

This tumor was estimated to constitute between one and one-half and five percent of all pulmonary carcinomas, the latter figure probably more nearly correct. The sex incidence is three males to two females. In one series of 155 cases, there were ninety-two males and sixty-three females. The youngest patient reported in the literature was a seventeen-year-old girl and the oldest was an eighty-three-year-old woman. The peak incidence is in the sixth decade. Family history and occupation are not known to be significant. There is little or no reference to the use of tobacco as a cause. Likewise, the past history is usually not enlightening.

Duration of Symptoms

The onset of illness in the majority of cases is gradual. The prevailing opinion is that this is not a rapidly debilitating disease, but a slowly progressive chronic pulmonary new-growth, that gives rise to remarkably few systemic symptoms, and usually kills by the sheer extent of the pulmonary involvement.

In a report of thirty-three cases, the average duration of symptoms before admission was four months.

Roentgenologic Findings

The X-ray appearance is not pathognomonic of bronchiolar carcinoma. However, in almost all reported cases, definite evidence of pulmonary disease was seen. The early lesions are usually light, patchy infiltrations, which become nodular lesions, usually multicentric, often coalescent to the point of forming a mass or massive pneumonic consolidations. Pleural fluid is present in ten per cent of the cases as reported by Decker. In general, the changes in the lungs are more extensive than X-ray appearance suggests.

Bronchoscopy and bronchography have proved of little value. The bronchograms may show evidence of incomplete filling of the bronchial tree in the involved portion of the lung, but with no evidence of an intrabronchial lesion.

Differential Diagnosis

This lesion may be confused with a chronic pneumonitis, tuberculosis, pulmonary abscess, chronic fibrosis, pulmonary edema, sarcoid, metastatic carcinoma, fungus or Hodgkin's disease.

Pathology

Grossly, bronchiolar carcinoma appears in two forms: (1) nodular, with multiple growths distributed throughout one or both lungs, and (2) diffuse in form, suggestive of coalescence of the nodules. Both forms may occur in the same patient. The nodules are a few millimeters to marble size; grayish, pink or whitish in color; firm with sharply defined borders. The diffuse form resembles a lobar pneumonia in a stage of gray hepatization involving a lobe or even the entire lung. The appearançe suggests development from multiple foci. There is no involvement of bronchi or bronchioles with tumor. The absence of primary involvement of the major bronchi is a striking gross finding, although secondary invasion of the bronchi by large tumor may occasionally occur.

Microscopically, there is some variety in the appearance. The cells may be of tall columnar or cuboidal type with pink-staining nuclei and dark, hyperchromatic nuclei. A prominent feature is that the interalveolar septa are lined but not invaded by the cells. Commonly, papillary projections into the lumen of the alveolar spaces are seen.

Diagnosis

Early diagnosis is difficult. The clinical signs and symptoms may not appear until late; none of the symptoms are characteristic. The roentgenologic finding is an important clue. Bronchoscopy and cytologic examination of the bronchial washings is of limited value for reasons already mentioned. In most cases, thoracotomy is the only way to establish the diagnosis.

Treatment

Surgical resection is the only hope for cure. Various operations — lobectomy, segmental resection, and radical pneumonectomy have been used; the last procedure utilized in the presence of hilar node involvement. It has been reported by some workers that this tumor does not metastasize early.

Radiation and chemotherapy have been used in inoperable cases with poor results. This tumor has been found to be resistant to radiotherapy.

Because of the multicentric nature of this tumor and because it frequently does not metastasize widely, the ultimate cause of death in many patients is pulmonary insufficiency. For this reason several authors have suggested limited surgical excision in order to preserve as much pulmonary tissue as possible.

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Instantaneous decisions are made often easily because they are not deflected by thought.—S. N. Behrman

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Clinical Path Conference

Suspected Myocardial Infarction

A single 43-year-old male laborer presented as an emergency admission. Five days previously he had been seen by his private physician for symptoms of the "flu" and was advised to take time off from his work and rest at home. This he did; but he continued to feel 'poorly' and therefore decided to enlist the care of his sister. During the trip by auto to her home, he felt progressively worse and called her to meet him en route. When she arrived he was extremely ill and was immediately brought to the hospital.

Physical examination showed a thin, but well-developed male who appeared in extremis. He was stuperous and areflexic. Blood pressure was 90/?; respirations were 32 per minute; temperature was normal. Facies was yellow, sallow and drawn; eyes were sunken; mouth was dry and tongue coated. Neck vessels appeared distended. A few posterior basilar rales were present. Heart sounds were distant. Extremities were cold and cyanotic.

On the basis of the initial electrocardiogram (Fig. 1) an anterior myocardial infarction and borderline bundle-branch block were suspected. Nasal oxygen, morphine sulfate, Papaverine and 100 mg. Cortef were given; Levophed intravenously was started to maintain blood pressure. Throughout the night he was nauseated and coughed occasionally. Extremities remained cold and cyanotic. Severe diaphoresis and Cheyne-Stokes respirations developed. At 5:30 a.m. on the second day his blood pressure dropped to 0/0. Levophed administration was then increased and 100 mg. Cortef were given. He appeared in extremis and relatives were called; but by 8:30 a.m. blood pressure had risen to 110/80 mm. Hg. Crystodigin medication was started and Levophed continued. By 5:00 p.m. he was awake and alert, taking oral fluids, and his skin was warm. At 11:00 p.m. he was comfortable, and urine output for the first time was up to 60 cc. per hour.

Laboratory data obtained during the day revealed the hemoglobin to be 14 gm. %, leucocyte count 27,100 with 95% neutrophils and 5% lymphocytes. Sedimentation rate was 22 mm. per hour and serum transaninase

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44 units. Chest X ray showed the heart at the upper limit of normal. No infiltrates were seen. Slight pulmonary congestion was present. A repeat electrocardiogram was similar to the initial one.

On the third hospital day Levophed was discontinued and 5 mg. of aramine per hour started, with additional administration as needed. At 4:00 p.m. chills and perspiration began. By 5:00 p.m. the blood pressure was 90/? mm. Hg., remaining so throughout the night and following day despite large amounts of aramine. Urine output was 675 cc. for 24 hours. Leucocyte count was 13,000. Electrocardiogram was thought to show less acute change.

On the fifth hospital day the patient again appeared in extremis. Aramine was increased and 100 mg. of Cortef given. Blood pressure remained 90/? mm. Hg. for several hours, then rose to 110/90 mm. Hg., where it was maintained throughout the following day. Furadantin therapy was started because of dysuria and a rectal temperature of 100.6° F. Urinalysis revealed a specific gravity of 1.024 and 1 plus hyaline casts. BUN was 81 mg. %, serum sodium 118 mEq per liter, potassium, 6.6 mEq per liter, chloride, 118 mEq per liter. Vasopressor agents were discontinued.

By the seventh hospital day heart tones were stronger and blood pressure stable at 96-122 mm. Hg. systolic without vasopressor. The patient was clear when awake. Morphine was given for pain in the chest and right arm but no vasopressors were administered. At this time the leucocyte count was 16,500 per cubic mm., electrocyte sedimentation rate 69 mm. per hour, BUN 90 mg.%, and serum bilirubin 0.7 mg.%. Urine output was 1,440 cc. for 24 hours. On the eighth hospital day he was alternately alert and sleepy. Blood pressure was stable, urine output 1,380 cc., leucocyte count 10,450.

On the ninth hospital day at 11 a.m. a large brownish emesis occurred. By 2:00 p.m. blood pressure was recorded at 90/68. At 5:00 p.m. the patient was sweating profusely. At midnight the blood pressure had fallen to 80/34 and Aramine was again started. Urine output during this day had fallen to 665 cc. During the night and the following day the blood pressure was barely detectable. Temperature was 101° F. and the BUN was 70 mg.%.

By the eleventh hospital day the patient was again afebrile. Despite the use of Vasopressors, however, blood pressure could not be maintained. Leucocyte count was 14,400, electrocyte sedimentation rate 66 mm. per hour, and urinary output 623 cc. in 24 hours.

Restlessness continued during the twelfth hospital day. The maximum blood pressure reached was 94/64 mm. Hg. Leucocyte count was 10,200 mm. and urinary output 617 cc. for 24 hours. BUN had risen to 93 mg. %.

On the thirteenth day the temperature rose to 102° rectally and the patient expired.

Discussion

Robert A. Maslansky, M. D.

At the outset I should like to make some comments with regard to the prodromal manifestations of "flu": This is a ubiquitously used term, and in my mind it conjures up a patient with certain subjective manifestations as well as a clinical appearance. I envision "flu" victims to be suffering from a combination of malaise, fever, chills, and myalgia. Frequently they have an upper respiratory infection characterized by a bronchitic type of pain. A relative specific for the management of "flu" is the use of acetylsalicylic acid and fluid encouragement. Suppose then we have a man who has this spectrum of complaints: a worker who may not have been assiduously careful of his health in the past.

Sudden Progressive Illness

Suddenly he gets sicker. He is admitted to the hospital in shock, markedly dehydrated, and described as being yellow . . . but not jaundiced. A little later we are told that he is cyanotic. Actually, he is a combination of yellow and blue, which, if I recall my primary colors properly, will produce a green hue.

Electrocardiographic Changes

The electrocardiograms can be considered next. The initial cardiogram (Fig. 1) has a prolonged duration of the QRS, with a frontal plane axis of 120°. There is a late R in AVR; a 2-3 mm. elevation of the ST segment of V-2 and V-3, and a rather striking peaking of the T waves throughout the precordium. This early tracing suggests hyperkalemia, and it may raise the question of an anterior injury as well. Subsequent cardiograms show diminution in the hyperkalemic manifestations, and by the third cardiogram, the so-called injury current is gone. The serial cardiograms can be interpreted as waning hyperkalemic effect.

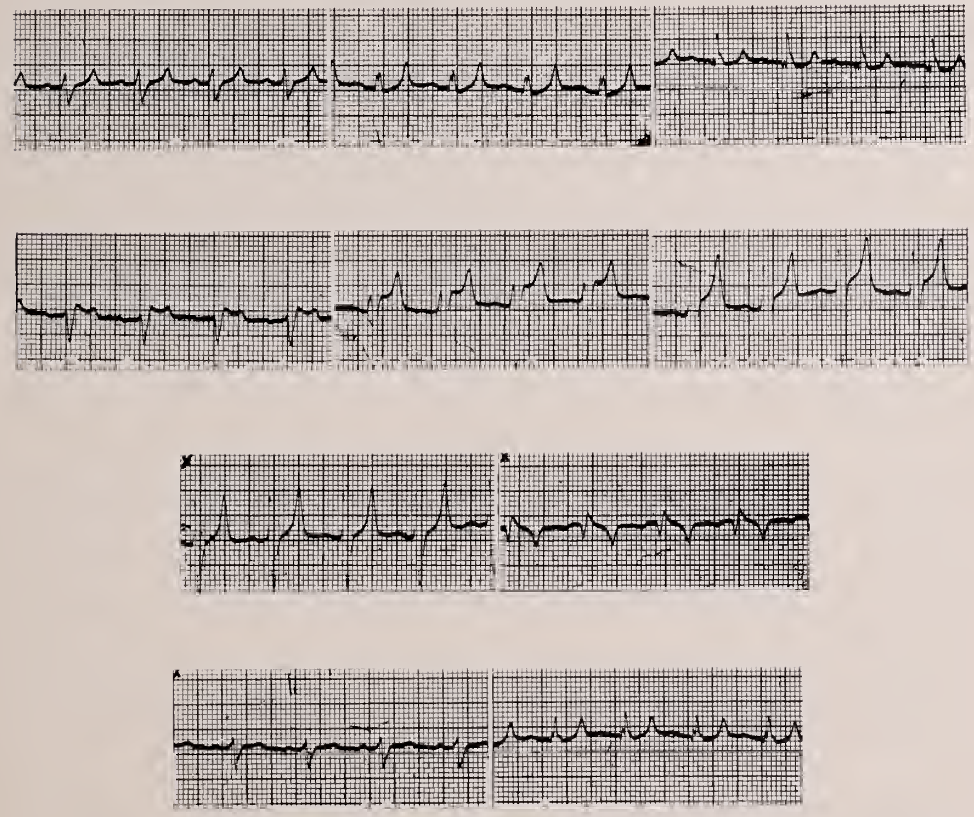

Fig. 1

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Hyperkalemic Changes

Among the hyperkalemic electrocardiographic changes peaking of the T waves is the striking and characteristic feature. However, there are ancillary manifestations of increased potassium concentration. Not infrequently, there is also an increased duration of the P wave, decreased speed of intraventricular conduction, resembling a bundle-branch block phenomenon, and a decrease in the total QRS-T interval.

Clinical Progress

The patient was treated for shock. Morphine sulphate and oxygen were administered as well as vasopressor substance and soluble hydrocortisone. Papaverine was also given. At first blush one wonders about the probity of the use of Papaverine in shock. Papaverine is a peripheral vasodilator, and it has been suggested that it is a central vasodilator and coronary vasodilator as well. Its use here is predicated by the diagnosis of acute anteromyocardial infarction. In the past there has been some enthusiasm for it in occlusive coronary artery disease, but hypotension is a contraindication. The striking feature in the patient's second hospital day was his ostensible response to the regimen initiated, which, I should like to point out, may have been related to the infusion of vasopressors and/or Cortef. The patient was rapidly digitalized. The remainder of the hospital course was characterized by waxing and waning hypotension. The one consistent feature is that in each instance where Cortef was infused there was some improvement.

Laboratory Evaluation

Blood Values

An initial hemoglobin of 14 was probably spuriously elevated because of his dehydration. The same may be said for the initial leukocytosis of 27,100, because when he became better hydrated, the white count settled down to a range between 10 and 16 thousand. The three sedimentation rates: 22 on the first hospital day, 69 on the seventh hospital day, and 66 on the eleventh hospital day, did not help.

Urine Values

The record of the patient's urinary output, especially from the seventh hospital day on, indicates a rather dramatic fall-off on the ninth day, from a level of about 1300 cc. to 600 cc. each day. A urinalysis was done on the sixth hospital day, showing a specific gravity of 1.024 with hyaline casts present. I would have you keep in mind the specific gravity of 1.024 and reflect on it in the context of what was ostensibly an azotemic state. We are told that the BUN was 81 mg.% on the sixth day, 90 mg.% on the seventh day, 70 mg.% on the eleventh day. The ancient, nonetheless clinically usable, division of azotemia into pre-, intra-, and post-renal etiologies can be used here. In the face of an excellent concentration and reasonable good urinary output, one can say that this patient's urea nitrogen was high, not because of renal disease, but rather because of an accelerated catabolism. The kidneys could not handle all of the urea with which they were presented. Also total renal blood flow must have been diminished because of shock.

Electrolyte Values

Now we get to the electrolyte studies: These are profoundly altered: a sodium of 118 meq./liter, a potassium of 6.6 meq./liter, and a serum chloride of 118 meq./liter. The patient had a marked hyperchloremic acidosis. The feature of this electrolyte profile that needs explanation is an anomalous elevation of the potassium in the face of a good urine output and excellent specific gravity. Endogenous alteration of the serum potassium with good urine output is most unusual. This is especially true when the kidneys are apparently functioning well enough to concentrate the urine. This directs our attention to a nonrenal cause for hyperkalemia. It is of interest to note that the sodium was profoundly depressed as well. Thus we can see that the electrolyte pattern is consistent with a nonrenal hyperchloremic acidosis, a profound hyponatremia, and a significant hyperkalemia. The situation that can provoke this change is but one: adrenal insufficiency.

Comments

I am postulating that this patient was an Addisonian. I am prepared to tie in the clue that he had a yellow complexion with this diagnosis by simply stating that yellow is not so far from brown. I am also prepared to support my diagnosis with the claim that this electrolyte composition is to be found in no other situation. Moreover, the curious response to infusions of Cortef suggests that this meager replacement therapy was efficacious for the times when it was given. Other diagnoses that could be entertained, but rather rapidly dismissed for want of evidence are: (1) the syndrome of inappropriate excretion of antidiuretic hormone, more frequently associated with the common denominator of increased intracranial pressure, either secondary to chronic pulmonary disease, (respiratory acidosis and intracranial pressure), or spacetaking lesions of the cranial vault which produce increased intracranial pressure. There is no evidence that this was the case here. Moreover one usually finds a dilutional hyponatremia associated with hypokalemia and hypochloremia. Finally, (2) brief consideration can be given to the diagnosis of a salt-losing nephritis. However, salt-losing nephritides are ordinarily much more chronic, and again one rarely sees hyperchloremia in such instances. Further, it would be difficult to explain the hyperkalemia on this basis.

My final diagnosis is Addison's disease, etiology not apparent. On a statistical basis one must assume that in 1962 this patient had idiopathic adrenal atrophy. However, it is not so difficult to conjure up a tuberculous or histoplasmotic etiology for his adrenal destruction.

B. F. Woolfrey, M.D.

I would like to thank Dr. Maslansky for his fine discussion of this case. The autopsy findings were as follows. Both pleural spaces were almost completely obliterated by fibrous adhesions. The lungs exhibited a few small apical, focal parenchymal scars but were otherwise unremarkable. The heart weighed 325 grams and appeared entirely normal. The coronary arteries were remarkably free from arteriosclerotic changes and no occlusions were found. The adrenal glands presented striking gross pictures (Fig. 2), both being enlarged to approximately two to three times the normal size and quite firm and nodular. On cut section the medullary and

Continued

cortical areas were almost completely replaced by pale tan-yellow material which was hard and not caseous. Only a few yellow focal remnants of cortical tissue were found about the peripheries. Microscopical examination revealed almost total adrenal destruction by active confluent granulomas (Fig. 3). Acid-fast bacilli were easily demonstrated in these lesions. Except for congestion and signs of longstanding hypotension, the other organs were unremarkable. No tuberculous focus elsewhere was found. One might

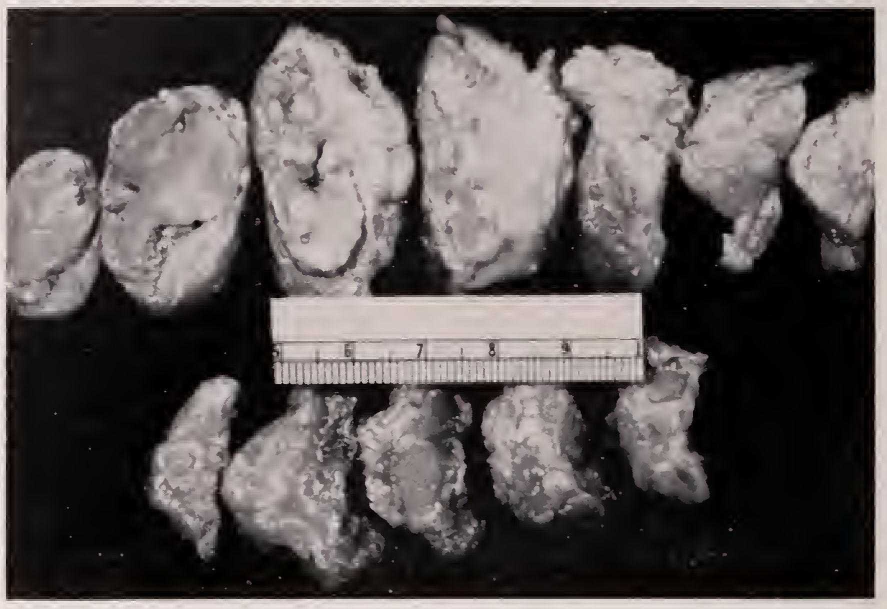

Fig. 2 — Gross photographs of adrenals which have been sectioned to show their essentially replacement by inflammatory tissue.

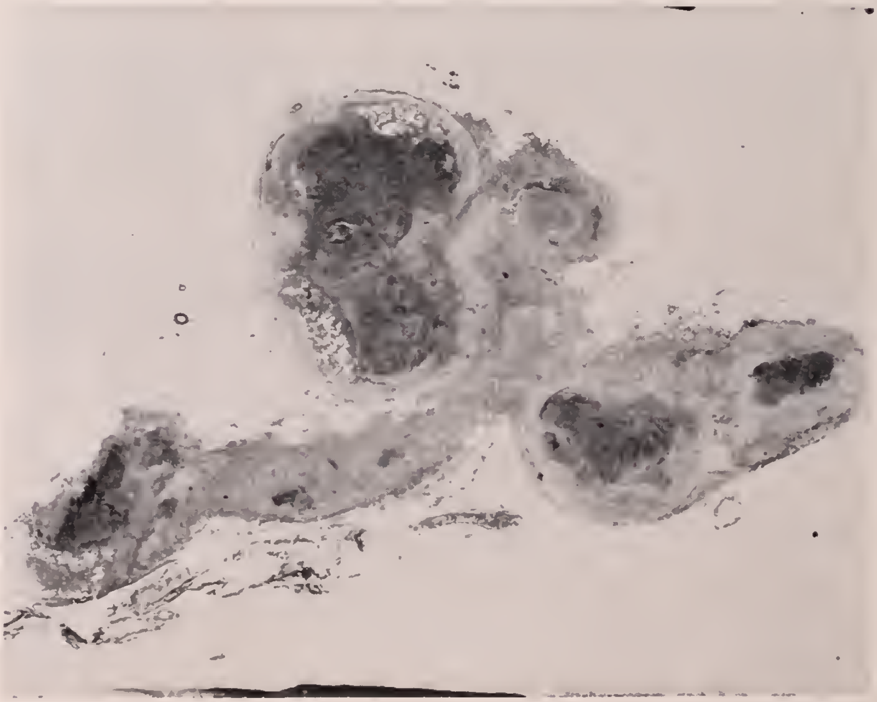

Fig. 3 — Low power photomicrographs showing almost total replacement of the adrenal cortex with tuberculous granulomas.

speculate on the possibility that the pleural adhesions and pulmonary scars were residuals of tuberculosis, but definite evidence for this was not demonstrated.

From the autopsy findings one must conclude that this man suffered from severe adrenal insufficiency of a subacute or chronic nature. It is likely that some stress-producing event, as suggested by Dr. Maslansky, pushed him into an acute adrenal crisis. The "flu"-like symptoms may have been manifestations of a precipitating infection but are also compatible with the early symptomatology of acute adrenal insufficiency. In any event, we have no anatomical evidence that points to the initiating process.

Subacute or chronic adrenal insufficiency in our present medical era can be due to a number of causes. Tuberculosis has now taken second place to so called "idiopathic atrophy." In this latter entity, the adrenals are generally very small, sometimes grossly difficult to find, and microscopically they show loss of cortex, presumably from necrosis of cells. Etiologic speculations for this process have included viral, toxic, and antoimmune mechanisms, but the term "idiopathic" best explains the present status.

Granulomatous processes, of which tuberculosis accounts for the vast majority, are found in approximately 40% of cases. A primary infection elsewhere can usually be found. A small percentage of cases can be accounted for by other causes, such as metastatic tumor, administration of steroids with suppression of adrenal function, trauma, hemochromatosis, and amyloidosis.

Final Diagnosis: Bilateral tuberculosis of adrenal glands with adrenal insufficiency.

Robert A. Maslansky, M.D.
B. F. Woolfrey, M.D.
Hennepin County General Hospital

Pliny's* Treatment for Pain in the Abdomen

Pliny observed that for the gratification of the belly the greater part of mankind exist, and this likewise causes most of the suffering. He says that "at one time it will not allow the aliments to pass, while at another it is unable to retain them." He refers to the over-indulgence of food as being "the excesses practiced at the present day" and that "through these dissipations more than anything else man hastens his end. This receptacle, more troublesome to us than any part of the body, is ever craving like some importunate creditor. No wonder, then, that the belly should have to be indebted to the aid of medicine in the very highest degree."

For stomach disorders he recommended Scordotis, freshly gathered and beaten, administered in doses of one drachma, with wine, to arrest diarrhea. "For coeliac affections, betony** is taken in astringent wine, or iberis*** is applied topically For tenesmus, root of nymphaea heraclia† is taken in wine. The juice of aixoum# arrests diarrhea and dysentery and expels round tapeworm."

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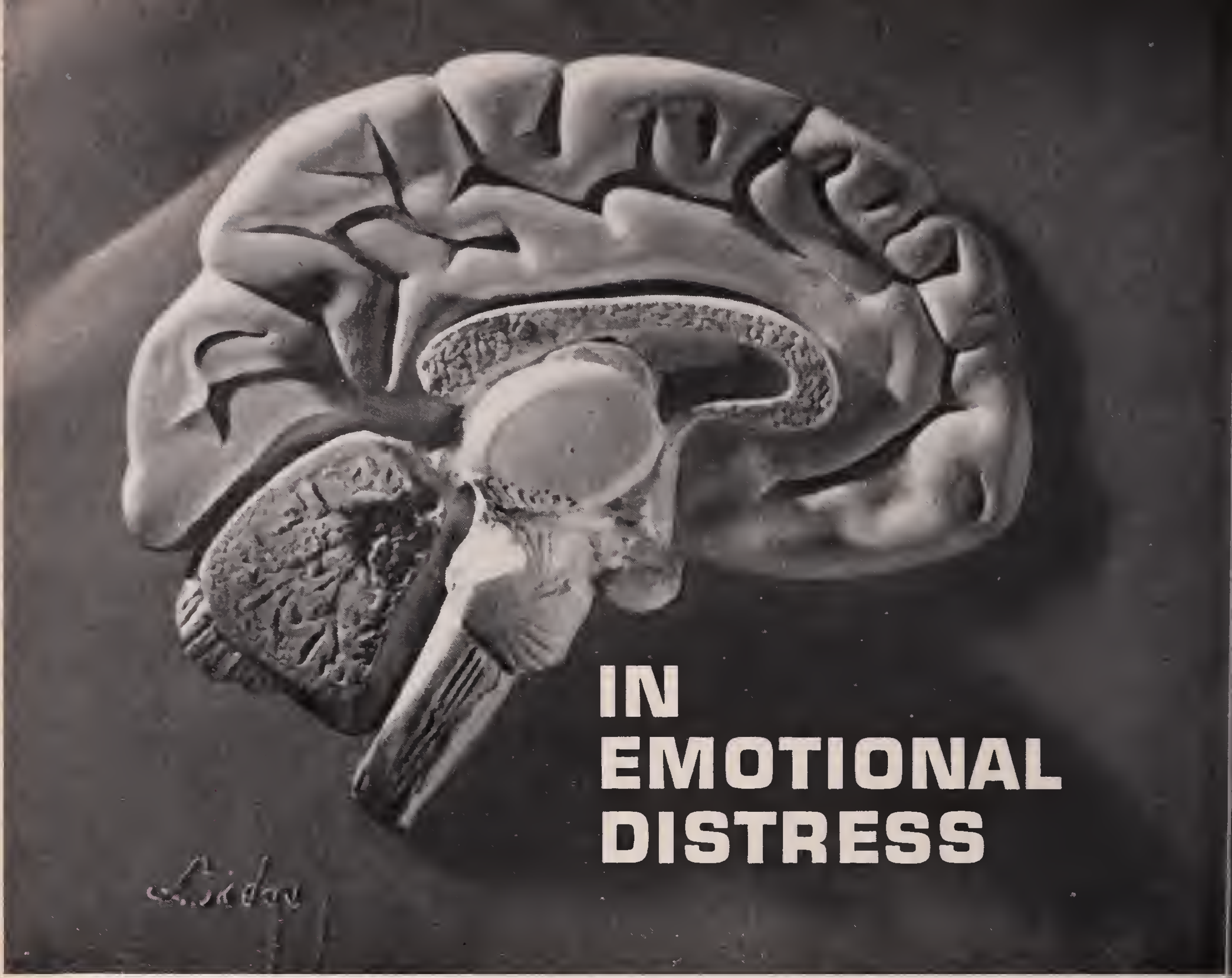
*See Minnesota Medicine June, 1964, Page 716.

**A plant. The tops are astringent and aromatic; the roots are emetic and cathartic.

***Candytuft- flat topped clusters of white or purplish flowers.

†Water lily. The root is astringent.

#A low plant from the Mediterranean with yellow flowers and silvery foliage.



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CME-1969

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Antibacterial Therapy

III* Newer Observations on the Older Agents

WILLIAM J. MARTIN, M.D.*
Rochester, Minnesota

USE OF 4,000,000 units of penicillin V given orally in four divided doses beginning twenty-four hours preoperatively appears to be as effective as other forms of penicillin given on differing schedules in decreasing bacteremia after oral surgical procedures.[1]

Penicillin V

Penicillin V given in amounts of 125 mg. (200,000 units) to 250 mg. (400,000 units) two to four times daily the first week of each month may prevent recurrent lymphangitis and consequent lymphedema in patients who have congenital or postoperative abnormalities of the lymphatic system. Progression of the lymphedema may thereby be prevented. Benzathine penicillin G in amounts of 1,200,000 units given intramuscularly once a month also appears to be effective. Erythromycin may be employed for individuals who are allergic to penicillin.[2]

Neomycin

Malabsorptive Effects

Neomycin administered by the oral route may produce malabsorptive effects resembling those found in nontropical sprue.[3] These effects include steatorrhea, azotorrhea, and interference with the absorption of vitamins, sugars, and minerals. These malabsorptive effects are produced by doses commonly used to suppress the fecal flora, as in certain patients having hepatic coma. It is wise to consider them in one's management of such cases, since there may be jeopardy from drug-induced dietary privation.

Respiratory Arrest

Neomycin instilled intraperitoneally has been followed by respiratory arrest. Instillation of more than 2 mg./kg. of neomycin in the peritoneal cavity of the narcotized, anesthetized patient is to be avoided. There is evidence that this effect results from peripheral curare-like neuromuscular blockade, rather than from central respiratory depression. Aspiration of the bulk of the solution at the end of the operation reduces the hazard of apnea or respiratory arrest.

Neuromuscular Block

In addition to neomycin, at least three other antibacterial agents, namely, streptomycin, polymyxin B, and kanamycin, are capable of producing neuromuscular block similar to that produced by D-tubocurarine.[4] Curare-like effects may be noted soon after instillation of these drugs either intraperitoneally or intrapleurally. The large surface area the pleura and peritoneum afford, which allows for the rapid absorption of these drugs, may be an important factor in the genesis of the effects. Similar effects have followed intravenous administration of kanamycin, and this might alert one to the possibility of their appearance when polymyxin B is given by that route. Neostigmine, 0.25 mg. given intravenously with the dose titered

Continued

See #I, II, Minn Med May Issue, 1964, Page 577 and June Issue, 1964, Page 717.

**Section of Medicine, Mayo Clinic and Mayo Foundation.

upward as necessary, may control neuromuscular block following the use of neomycin, streptomycin, and kanamycin. Calcium gluconate may be preferable when the ill effects follow use of polymyxin B. Anoxia, sometimes associated with anesthesia, may enhance the occurrence of antibiotic-induced curare-like effects. Failure to reverse the untoward reaction may eventuate in respiratory and cardiac arrest. Possible reinforcement of the neuromuscular block is an additional reason for avoiding simultaneous use of the responsible antibacterial agents.

Depression of Normal Flora

Neomycin as well as streptomycin, sulfonamides, and other antimicrobial agents which, like the tetracyclines, may depress the gram-negative elements of the normal flora may thereby allow overgrowth of resistant staphylococci. In addition to staphylococcal enterocolitis, bacteremia, pneumonia, and other staphylococcal superinfections may occur.[5]

Kanamycin

The recommended daily dose of kanamycin by the intramuscular route for an adult patient of average weight (150 pounds) is 1.0 gm. and should not exceed 1.5 gm., even for heavier patients. Equally divided doses are given two to four times daily. If definite response does not occur within five days, therapy should be stopped. In all cases one should be hesitant to continue therapy beyond ten days. These limitations on dosage are urged because of the toxic potential of the drug, especially its ototoxicity.

Chloramphenicol, Streptomycin, Isoniazid

Optic Neuritis

Chloramphenicol, streptomycin, and isoniazid are three antimicrobial agents which appear to have caused optic neuritis. Ancillary data[6] suggest that these drugs may induce pyridoxine deficiency, which results in lesions of the optic nerve. If further investigation confirms drug-induced alteration in pyridoxine metabolism in such cases, patients receiving these agents may require supplements of pyridoxine.

Pyridoxine Deficiency

Pyridoxine deficiency may be manifested by anemia and convulsions in addition to neuropathy. If the hypothesis concerning the genesis of optic neuritis following use of chloramphenicol, streptomycin, and isoniazid is correct, one should be alert to the possible occurrence of additional manifestations of pyridoxine deficiency in patients receiving these drugs. Also, since cycloserine has caused convulsions, which appeared to be prevented or controlled by administration of pyridoxine, one should be aware of the theoretic occurrence of anemia and neuropathy, peripheral as well as optic, in patients receiving the drug.

Gray Syndrome

Administration of chloramphenicol to infants has resulted in abdominal distention, lethargy, respiratory distress, and gray cyanosis ("gray syndrome"). Use of the drug should be discontinued promptly since this syndrome may be fatal. The syndrome appears to reflect excessive concentration of chloramphenicol in the blood, deficiencies of drug conjugation, and poor renal function in the infant. To avoid excessive serum levels in infants, not more than 25 mg./kg. per day should be given them in those rare instances when use of chloramphenicol is imperative.

Suppression of Bone Marrow

In certain individuals, chloramphenicol-induced suppression of the marrow may represent an accentuated normal response to the drug since mild reversible changes are not rare, and large doses given for prolonged periods will cause maturation arrest in a number of subjects. The metabolic handling of chloramphenicol has been studied in some patients having recovered from chloramphenicol-induced suppression of the marrow, and the drug was found to have been detoxified and excreted by them in a normal manner. There appears to be no correlation between the metabolic products of chloramphenicol and marrow depression; the marrow depression rather appears to reflect high levels of free chloramphenicol in serum and plasma. Rising serum iron levels and reticulocytopenia may be helpful indices of chloramphenicol-induced hematotoxicity. A greater incidence of marrow depression due to chloramphenicol may occur in patients having hepatic or renal insufficiency. In other individuals, hypersensitivity may play a role, but perhaps such a reaction is not an all-inclusive explanation for the hematotoxic effects of chloramphenicol.

Tetracyclines

Photosensitivity

Photosensitivity, while more frequently associated with the use of demethylchlortetracycline, was reported early in the experience with chlortetracycline[7] and more recently on administration of tetracycline[8] and of oxytetracycline.[9] Along with the tetracyclines, griseofulvin and certain sulfonamides may be photosensitizing.

Discoloration of Teeth

Tetracyclines can result in yellow, gray, or brown discoloration of children's teeth, primarily after prolonged treatment.[10-12] Initially the color is bright yellow, and then it turns brownish with increasing age; perhaps exposure to light intensifies the pigmentation. When the second teeth are afflicted, the discoloration appears to be permanent. Pigmentation has followed use of the drugs either by the mother in late pregnancy or by the child during the period of tooth development. The discoloration tends to affect the same teeth on both sides of the jaw. Pigmentation appears to occur first on the gingival margin. In children whose deciduous teeth are discolored by the absorption of tetracycline in utero, the permanent teeth should not be discolored if tetracycline is not given to the child during the first two years of life, when the permanent teeth are being calcified. When pigmentation of deciduous teeth is severe, there may be associated deformity of the canines and molars, with the affected teeth having sharp cusps because of faulty enamel formation. The pigmented teeth show characteristic fluorescence and histologic findings.

The tetracyclines are deposited in teeth and bones apparently because of the chelating properties of these agents and formation of a tetracycline-calcium-orthophosphate complex. The question has been raised whether deposition of the drugs in bones might inhibit their linear growth in premature infants.[13]

Discoloration of Nails

In patients having received prolonged therapy with the tetracyclines, fluorescence of the proximal part of the nails may be demonstrable. Sometimes significant discoloration of the nails and onycholysis can be seen by the naked eye.[8,10]

Antianabolic Effect

The tetracyclines can produce an antianabolic effect manifested by weight loss; increased urinary loss of nitrogen, sodium, and riboflavin; negative nitrogen balance; and increased azotemia, hyperphosphatemia, and acidosis which may have significant clinical ramifications in patients who have reduced renal function.[14] Because renal insufficiency tends to increase the serum concentrations of tetracyclines, reduced dosage to avoid supervention of this syndrome is advised. The antianabolic action of the tetracyclines, which apparently reflects inhibition of amino-acid incorporation into protein, does not appear to have great significance in patients with adequate renal function, although its manifestations in them are detectable by metabolic studies.

Fanconi Syndrome

A reversible Fanconi syndrome can result from the ingestion of outdated or degraded tetracycline.[15,16] Polyuria, vomiting, lethargy progressing to coma, proteinuria, glycosuria, hyperphosphaturia, hypercalciuria, aminoaciduria, hypophosphatemia, hypokalemia, hyponricemia and acidosis may occur. An acquired or adult-type Fanconi syndrome also has been attributed to multiple myeloma and heavy-metal poisoning. Since Bence-Jones protein has been noted in the urine of a patient who ingested outdated tetracycline, diagnostic confusion regarding the cause of the acquired Fanconi syndrome is possible. A degradation product of tetracycline such as

Continued

epianhydrotetracycline or anhydrotetracycline currently is suspected as the etiologic factor in the inhibition of tubular reabsorption. Both physician and patient should be aware of the necessity for discarding unused tetracyclines in keeping with the manufacturer's expiration date.

Tetracycline stored under extreme conditions of heat and humidity also may give rise to degradation products that are potentially capable of inducing a Fanconi syndrome. Among the factors on which the rate of tetracycline degradation appears to be dependent are temperature, humidity, pH, and the presence of various fillers and excipients. An important observation is that in the presence of alpha-lactose monohydrate, tetracycline shows decreased degradation in accelerated stability studies using severe test conditions. The packaging of tetracyclines with lactose for commercial distribution is contemplated, since the antibacterial effectiveness of the drug appears not to be reduced thereby.

Transitory Myopia

Tetracycline, like the sulfonamides, has been said to have caused acute transitory myopia. Since the reaction may reflect an allergic mechanism, use of an antihistaminic agent in such cases has been suggested.[17]

Resistant Streptococci

Because there appears to be significant resistance of beta-hemolytic streptococci to the tetracyclines, these agents may not be acceptable substitutes for management of infections due to these organisms in patients who are unable to accept penicillin. Specifically in so-called streptococcal sore throat due to such resistant bacteria, the tetracyclines may not prevent complicating rheumatic fever or glomerulonephritis. In patients who have such infection and who are allergic to penicillin, erythromycin is a better substitute.

Erythromycin

Hepatotoxicity

Evidence of hepatic dysfunction has appeared in some cases after a few days of treatment with erythromycin estolate,[18] but generally this has followed one or two weeks of continuous therapy or several courses of the drug. Jaundice, abnormal results of liver function tests, and eosinophilia may occur, but the findings usually subside rapidly when use of the drug is stopped. Symptoms reappear promptly if the drug is readministered, usually within forty-eight hours. It appears that erythromycin, which is not hepatotoxic in its basic form, acquires this capacity by esterification of a side chain, that is, when a simple hydroxyl group is replaced by the propionyl radical. The effect seems to be one of intrahepatic cholestasis resulting from a form of sensitization. Until more data are available, use of either the erythromycin base or erythromycin stearate appears preferable unless circumstances in the individual case are extraordinary.

Recent experience indicates that triacetyloleandomycin, like erythromycin estolate, is hepatotoxic.[19] The side chains esterified in both antibiotics are similar; and, as aforementioned in the case of erythromycin estolate, when a hydroxyl group is replaced, as by the acetyl radical in the case of oleandomycin, the agent becomes hepatotoxic. While erythromycin base may be an adequate substitute for its chemical derivative in most of the infections requiring use of such a drug, oleandomycin is not sufficiently effective to replace triacetyloleandomycin. Because alterations in liver function have occurred in some patients after two weeks or more of therapy with triacetyloleandomycin, its routine use is not recommended in the management of infectious diseases which may require more than ten days of continuous therapy. If therapy is to be continued beyond ten days, tests of liver function should be carried out. Evidence of hepatic dysfunction appears to be reversible shortly after discontinuation of the drug.

Depression of Coccal Flora

Use of erythromycin, novobiocin, and other antibacterial agents which, like penicillin, may depress the coccal members of the body flora, may thereby encourage the production of bacteremia, urinary infection, pneumonia, and the like by gram-negative bacilli. When such organisms are relieved of their natural ecologic antagonists, they are free to overgrow and invade areas normally forbidden them. By periodic examination of the sputum and stools, one may be able to detect antimicrobial-induced changes in the body flora in time to avert clinical superinfection.[20]

Effect on Ischemic Lesions

Tissues of ischemic limbs usually contain detectable amounts of systemically administered erythromycin, tetracycline, and penicillin. When sensitive organisms are present in infected ischemic lesions, administration of these agents may contribute to salvage of a limb.[21,22]

Novobiocin

In most adults, the scleral discoloration following use of novobiocin apparently reflects the transient deposition of a harmless pigment produced in the metabolism of novobiocin rather than of bile pigments. The yellow pigment also has been found in the plasma of patients receiving the drug, and its presence may interfere with determinations of serum bilirubin and the icteric index. In young children novobiocin may interfere with the conjugation of bilirubin, and, rarely, in adults the drug may have caused hyperbilirubinemia and impaired sulfobromophthalein excretion. When scleral discoloration appears during therapy, administration of the drug should be discontinued until the nature of the pigment can be ascertained. Pigmentation resulting from the metabolite of novobiocin, as distinguished from that of true jaundice, does not contraindicate continued use of the drug.

Furadantin

In patients receiving nitrofurantoin (Furadantin), especially in those with azotemia, polyneuropathy is a rare possibility; and if numbness or tingling occurs at any site, administration of the drug should be discontinued immediately.[23]

Vancomycin

Currently, the chief use of vancomycin appears to be in patients with staphylococcal endocarditis who are allergic to penicillin. In patients who have such infection caused by penicillin G-resistant strains but who are not allergic to penicillin, vancomycin appears to have been displaced by methicillin as the drug most commonly employed. In general terms, the preference for methicillin appears to reflect the high incidence of pain and thrombophlebitis at the site of injection of vancomycin, the fear of the ototoxicity seen with vancomycin, and the fact that in patients with decreased renal function vancomycin must be given in reduced amounts or not at all. In patients with staphylococcal endocarditis who are allergic to penicillin and who cannot tolerate vancomycin, one may consider use of kanamycin, ristocetin, bacitracin, or sodium fusidate, alone or in combination with a bacteriostatic drug such as erythromycin, novobiocin, or chloramphenicol. Perhaps cephalothin or an allied cephalosporin C derivative will have potential application in patients having staphylococcal endocarditis.

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FANCONI'S SYNDROME

This syndrome may include a wide variety of birth anomalies, congenital defects, and associated hematologic and renal metabolic disturbances. It is thought that this represents a transmitted Mendelian recessive trait. There may be ecchymosis or hemorrhages occurring in the mucous membrane. Hyperpigmentation of the skin may occur as a result of hemosiderosis.

Remedies Derived From The Crocodile

The ashes of the skin of the crocodile, applied with vinegar to such parts of the body as are about to undergo an incision, will render the patient insensible to the knife. The blood of the crocodile, applied to the eyes, effaces marks upon those organs and improves the sight. The body, with the exception of the head and feet, is eaten, boiled, for the cure of sciatica, and is found very useful for chronic coughs, in children more particularly: it is equally good, too, for the cure of lumbago. — Pliny's Natural History.

Take Time TO BE FRIENDLY — It is the road to happiness.

Grand Rounds

Hepatic Porphyria

The term porphyria embraces a group of diseases, each one with unusual and characteristic clinical manifestations, which have in common the excessive excretion of uroporphyrins, coproporphyrins, or porphyrin precursors in the urine, the feces, or both. They are disorders of the porphyrin chemistry of the body, of which the striking clinical expression is often the passage of dark urine. They belong to that larger family of diseases called by Garrod "inborn errors of metabolism."

The porphyrin pigments are present in free or bound form in practically every cell of nearly all forms of life. They are characterized by a ring structure of four pyrrol nuclei and differ one from the other by virtue of the side chain attached to the pyrrol nuclei. The basic pigment of chlorophyll is actinoporphyrin, and that of homoglobin, protoporphyrin. The porphyrins are also vital components of enzyme systems such as the cytochromes and catalases. Thus porphyrins are possibly contemporaneous with the emergence of life itself.

The rather complex porphyrin molecule is synthesized in the body from two simple precursors, acetate and glycine. By an enzymatically controlled step delta aminolevulinic acid is formed, and under the action of aminolevulinic acid dehydrase is converted to porphybilinogen, which in turn, under the action of deaminase is transformed into uroporphyrinogen I, and, further, under the action of the deaminase and isomerase, into porphyrinogen III. Decarboxylation and subsequent dehydrogenation of the uroporphyrinogen I and porphyrinogen III lead to the formation of coproporphyrinogens, protoporphyrinogens and the corresponding porphyrins.

Porphyrin Synthesis

The synthesis of the porphyrins in the human body takes place mainly in the bone marrow and in the liver. In the bone marrow protoporphyrin III is present in the hemoglobin, and in the liver porphyrins participate in the formation of some heme enzymes such as cytochrome and catalase.

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*Presented as a Medical Grand Rounds at Mt. Sinai Hospital, Minneapolis, February 26, 1963.

Continued

Coproporphyrin

Normal urine contains a small amount of porphyrins. The predominant one is coproporphyrin, which is excreted at a daily rate of 100 to 300 micrograms, the value for males being distinctly higher than that for females. Protoporphyrin is normally absent from the urine but is present in bile and feces. It is necessary to point out that the total urinary coproporphyrin is increased under a great variety of circumstances, including heavy metal toxicity, leukemia, Hodgkin's disease, hemolytic anemias and pernicious anemia in relapse. Such coproporphyrinuria is related to the above mentioned diseases and does not belong to the group of porphyrias.

Porphyria may be divided into two general groups, porphyria erythropoietica and porphyria hepatica. In porphyria erythropoietica, excessive quantities of porphyrin are synthesized in the bone marrow; in porphyria hepatica excessive production occurs in the liver. This paper will refer to the symptoms and diagnosis of porphyria hepatica.

Porphyria Hepatica

Porphyria hepatica can be divided from the clinical viewpoint into at least three different types: acute *intermittent porphyria, porphyria cutanea tarda hereditaria,* and *porphyria cutanea tarda symptomatica.*

Acute Intermittent Porphyria

Acute intermittent porphyria is the most important member of the group and is clinically distinguishable from the others by the dominance of gastrointestinal and neurological symptoms and the absence of skin sensitivity. It is uncommon but not rare. The familial occurrence of the disease is marked and is probably transmitted as a Mendelian dominant characteristic. The most frequent age of onset is between 15 and 40, with a higher incidence in females. Some relatives of patients with acute intermittent porphyria, if screened for porphyrins in the urine, will show increased porphobilinogen; such persons, who have had no clinical manifestations of the disease, can be said to have latent porphyria.

Precipitating Factors in the Crises of Acute Intermittent Porphyria

Barbiturates

Since the introduction of the barbiturates into clinical medicine in 1903, there have been numerous conflicting reports in which they have been either accused or absolved of acting as precipitating agents of crises in acute intermittent porphyria

Genetic Defect

In the series of fifty cases reported by Goldberg and Remington two types of relationships were suggested between barbiturates and acute porphyria; first, if barbiturates are given to a person with the genetic defects predisposing to porphyria, they may precipitate an attack. In three cases, barbiturates were given for a period of time from eighteen months to two years. The presenting symptoms were drowsiness and memory loss, incoherence, convulsions, hysteria-like behavior, and depression. In each of the three cases the main symptoms and signs disappeared after the cessation of the drug, and there were no recurrences for several years. Therefore it seems probable that prolonged ingestion of barbiturates may precipitate an attack of acute porphyria where the latent trait exists, and in such cases the clinical manifestations resemble those of barbiturate intoxication. Second, there may be an association between the administration of barbiturates during an attack and the onset of paralysis. In the Remington-Goldberg series 77% of the cases with paralytic manifestations or paresis had been given barbiturates, while 35% of those without paralysis or paresis had taken barbiturates. This difference is significant ($P > .01$).

Menstruation

In many reports about the onset of the crisis in acute intermittent porphyria, menstruation and pregnancy have been implicated as precipitating factors. The influence of menstruation is not as yet well documented, because the incidence of cases in which it could be a factor has not been greater than the incidence which could be accounted for by chance. In addition, the occurrence of the disease in prepuberal males and postmenopausal women shows that if there is any association between menstruation and clinical symptoms, it is not a primary one.

Pregnancy

Vine, Shaffer, Pauley and Margolis reviewed 27 pregnancies in 16 women with porphyria. They found exacerbation of the disease in 21 pregnancies and spontaneous abortion in the rest of the cases. On the other hand, there have been cases reported in which pregnancy did not have any effect on the course of the disease, and other investigators have even reported improvement of the disease during pregnancy. Thus, at the present stage of our knowledge, it is impossible to state in unequivocal terms the exact relationship between pregnancy and the crises of acute intermittent porphyria until further evaluation of the many factors which may be involved clarify the inconsistent and even paradoxical relationship mentioned above.

Infection

It is well known that in many metabolic diseases (diabetes mellitus, and Addison's disease) the presence of infection may precipitate or aggravate an attack. Acute intermittent porphyria shows a similar relationship to infection in acute tonsillitis, urinary infection, skin infection and herpes zoster.

Alcohol

In the series of eighty cases of acute intermittent porphyria reported by Eales and Linder, overindulgence in alcohol preceded the crisis on six occasions, and one case of the same kind was reported by Goldberg and Remington.

Symptomatology of Acute Intermittent Porphyria

Gastrointestinal

Gastrointestinal symptoms are present in 90-95% of the cases. The classical triad of symptoms is formed by abdominal pain, vomiting, and constipation. The pain is sometimes very severe, steady or cramping, and

Continued

may appear anywhere in the abdomen, but it is felt mostly in the epigastrium and right iliac fossa. It also may radiate into the back, the thighs, and occasionally to the chest. The patient describes the pain as "deep down" and as causing great distress. It may last hours or even days.

The abdominal tenderness is much less than the severity of the pain would lead one to expect. There is no superficial pain, muscular rigidity, guarding, or rebound tenderness. Peristalsis may disappear. Rectal examination is generally negative. In all cases of severity there is loss of weight. Very often vomiting is present, as a rule preceding the pain. Constipation is very common, but in a few cases diarrhea has been present.

Neurological

The neurological symptoms almost invariably take the form of lower motor neurone paralysis, not necessarily starting in the lower limbs, however. Complaints of severe aching pain in the limbs precedes the development of the motor neuropathy. Motor weakness, flaccidity and loss of tendon reflexes are followed by severe muscular wasting, which may be extreme. The severe form has been misnamed an ascending paralysis of the Landry type. The degree of involvement need not be symmetrical, and occasionally distal involvement is more pronounced. Some tendon jerks may be hyperactive, but Babinski reflex is very rare. Sphincter disturbances are not uncommon.

The cranial nerves are involved in about 10% of the cases. Cranial nerves III, IV, V, VI, and VII have all been involved. Cerebral symptoms include headaches, focal and generalized seizures, aphasia, apraxia, and homonymous hemianopsia. Subjective sensory loss or paresthesias are frequent, but objective loss is uncommon and often patchy and irregular.

The early development of bulbar symptoms, such as dysphagia and dysphonia indicate a grave situation. Diaphragmatic and intercostal paralysis complete the picture. Although at this stage chances of recovery are slender, skilled and devoted care may avert death and permit eventual recovery, which in most cases is complete.

Psychiatric

The psychiatric manifestations are varied and may be the most prominent presenting symptoms. They usually precede the neurologic symptoms. Agitation, depression, disturbances of memory and of the sensorium with delirious and psychotic-like hallucinations and delusional experiences are among the most common.

Miscellaneous

Among the miscellaneous manifestations of acute intermittent porphyria, tachycardia, hypertension, faint jaundice and skin pigmentation can be mentioned. Increased frequency of micturition and dysuria may appear in about one quarter of the patients.

Laboratory Data in Acute Intermittent Porphyria

The freshly voided urine is frequently of normal color, but on standing in the sunlight turns to a burgundy-wine or even black color. This color change can be hastened by the addition of a small amount of acid and by boiling for thirty minutes. The explanation for these color changes is that colorless porphobilinogen is excreted in the urine, and not red uroporphyrin.

Porphobilinogen

The presence of porphobilinogen in patients with acute intermittent porphyria is a constant feature of the disease. During remissions the porphobilinogen reaction is usually positive, but a negative result does not exclude the diagnosis. The Watson-Schwartz modification of the Ehrlich reaction is a simple and very valuable screening procedure.

Traces of proteins in the urine are found in many cases, although this finding is not a constant feature of the disease. In some reports elevated urea values have been the rule during the attacks, and in over two thirds of the patients the peak urea concentration exceeded 50 mg. per 100 ml. Leukocytosis up to 12,000 is present in many cases.

Pathology of Acute Intermittent Porphyria

In the very few series of acute intermittent porphyria in which the outcome has been fatal, the peripheral and central nervous systems have been consistently involved. In rapidly fatal cases no lesion to correlate with the clinical picture has been found, probably because the damage to the tissues by the metabolic abnormality has not had enough time to produce detectable pathological changes. Elsewhere, patchy areas of demyelination with or without destruction of axis cylinders may be observed throughout the nervous system, including the peripheral nerves.

In the cerebral cortex, cranial nerve nuclei, spinal ganglia, and in the anterior horn, chromatolytic changes appear. In the cases in which severe hypertension has been one of the features of the clinical picture, the production of vascular lesions has resulted. The demyelination may affect the cerebellum white matter and the autonomic nerves.

The rest of the findings at autopsy are not related to the porphyria but to concomitant diseases that appear as complications in the course of the disease.

It is interesting to note that in the cases in which chemical analysis of the nervous system tissues has been carried out, the amount of porphyrins has not been greater than that normally present in such tissues. The samples of liver and kidney examined contained porphobilinogen, and the liver contained some uroporphyrin in the cases where this was looked for. In contrast, concentrations of coproporphyrin and protoporphyrin in the liver, bone marrow and spleen did not have appreciably higher values than in the tissue of controlled patients.

Pathogenesis of Acute Porphyria

Neurological

At present, the pathogenesis of the symptoms of acute porphyria can be explained on a neurological basis, the main gastrointestinal features as lesions of the preganglionic motor fibers that innervate the stomach. These fibers have their cells stationed in the spinal cord and medulla. Retrograde degenerative changes have been found in these nuclei. Demyelination of the vagus nerves and of fibers of the sympathetic chain have been noted in other cases. Nonabdominal pain, in the limbs and elsewhere, may be due to sensory fiber damage in the peripheral nerves; by the same mechan-

Continued

ism the presence of paralysis and paresis in the limbs can be explained. Finally, the lesions found in the white matter of the cerebellum and in the cerebral cortex and basal ganglia provide an explanation for the neuropsychiatric manifestations.

Liver

It is suggested that the fundamental disturbance of pyrrol pigment metabolism has its site in the liver. Associated with it is a related disturbance in the metabolism of the nervous system of which the demyelination is the pathological expression. The exact nature of the association between these two abnormalities is not yet clear. The elucidation of the porphyrin-like structure of vitamin B_{12} may have some relevance, particularly when it is realized that demyelination takes place in subacute combined degeneration of the cord.

Course and Prognosis

The course of the acute intermittent porphyria is variable. Some patients have occasional abdominal pain, while others have acute severe attacks with a duration of 10 days to 10 weeks. In general, the majority of cases lie between these extremes, attacks recurring for months or years.

This improvement in the mortality figures from 58% to 24%[1,2] seems to be due to the early recognition and possibly to the inclusion of milder cases.

Cutanea Tarda Hereditaria

The age of onset is between years 10 and 20, males and females being equally affected. The mode of inheritance seems to be by means of a non-sex-linked dominant gene. Here, as in the acute intermittent form, alcohol and barbiturates may act as precipitating factors.

Clinical Manifestations

The main clinical presentation in this disease is hyperpigmentation of the skin in light-exposed areas, often of a diffuse violaceous hue on the face and hands. The conjunctiva may be infected, even in nonalcoholic patients. The pigmentation may be mottled, and vitiligo of the hands has been noted. Edema, erythema, and vesiculation of the face, neck and hands as a result of exposure to light have been frequently described. The vesicles break, crust, and may become infected, giving an appearance of impetigo. The edema may be quite severe, sufficient to allow pitting on pressure. Pruritus of the affected skin is commonly present after exposure to light.

The affected areas may leave excoriations, crusts, scars, and sometimes a sclerodermoid, rugose appearance on the skin of the forehead or the back of the neck. The scarring may be so marked on the face and hands that gross deformity is caused.

Pathology

The most important findings have been in the skin. Different reports show the presence of hyaline swelling of the walls of the capillaries in the upper corium. The acid-Schiff stain reveals intense polysaccharide-staining of the basement membrane and swelling, even though there has been no exposure to sunlight for several weeks. Here, damage to the minute vasculature could account for the abnormal fragility of the skin. Holti, Remington, Tate and Thomas noted endothelial proliferation in nearly all vessels, almost obliterating the lumen of some capillaries, and perivascular cuffing with small round cells. Histological examination of the fresh vesicles of the hand show that the roof is formed by the entire thickness of the epidermis, and the inflammatory reaction is very poor. Other histological changes have been atrophy of the skin and heavy melanin deposits.

Hypertricosis

Hypertricosis is common in women. Hirsutism may involve the whole face, but more commonly it is prominent at the hair margins extending down to the cheeks. It may also be obvious on the arms and legs. Sometimes it is sufficiently marked to be the main symptom.

Increased Sensitivity of Skin

Increased fragility of exposed skin is an important manifestation and may be the only skin abnormality in subjects with the characteristic porphyrin dyscrasia. As a result of minor trauma, superficial layers of the skin may be abraded. Small blisters are common on the hands and on the elbows and knees where these are exposed. Some investigators have been able to induce bullous lesions by tapping the skin repeatedly with a stick. The skin lesions and even the whole skin may show a porphyrin fluorescence under ultraviolet light.

The outstanding biochemical feature of the disorder is the increased excretion of coproporphyrin and protoporphyrin in the feces at all times in the course of the disease. As in acute intermittent porphyria, either death or recovery may occur.

Prognosis

Porphyria cutanea tarda hereditaria carries a better prognosis than either congenital or acute porphyria. The tendency to skin photosensitivity may burn itself out after middle age, even though the porphyrin dyscrasia remains. Diminished activity and exposure to light in old age may contribute to this remission.

Porphyria Cutanea Tarda Symptomatica

In this type of porphyria hepatica the skin lesions are indistinguishable from those observed in porphyria cutanea tarda hereditaria. The skin is sensitive to mechanical trauma and to light. The disease is called symptomatic because it is a condition acquired and related to liver disease. It has been described in old people, 40 to 70 years of age, with alcoholic cirrhosis, in inhabitants of Turkey who had ingested the fungicide hexachlorobenzene, and in three elderly subjects with tumors of the liver. There is excretion of large amounts of uroporphyrin and lesser amounts of coproporphyrin in the urine. Abdominal tenderness and neurological manifestations are absent. The excretion of protoporphyrin in the feces is normal. Also excretion of coproporphyrin in the feces is usually within normal limits, but in a few patients may be slightly increased.

Prognosis

This form of porphyria hepatica is usually not fatal unless liver function

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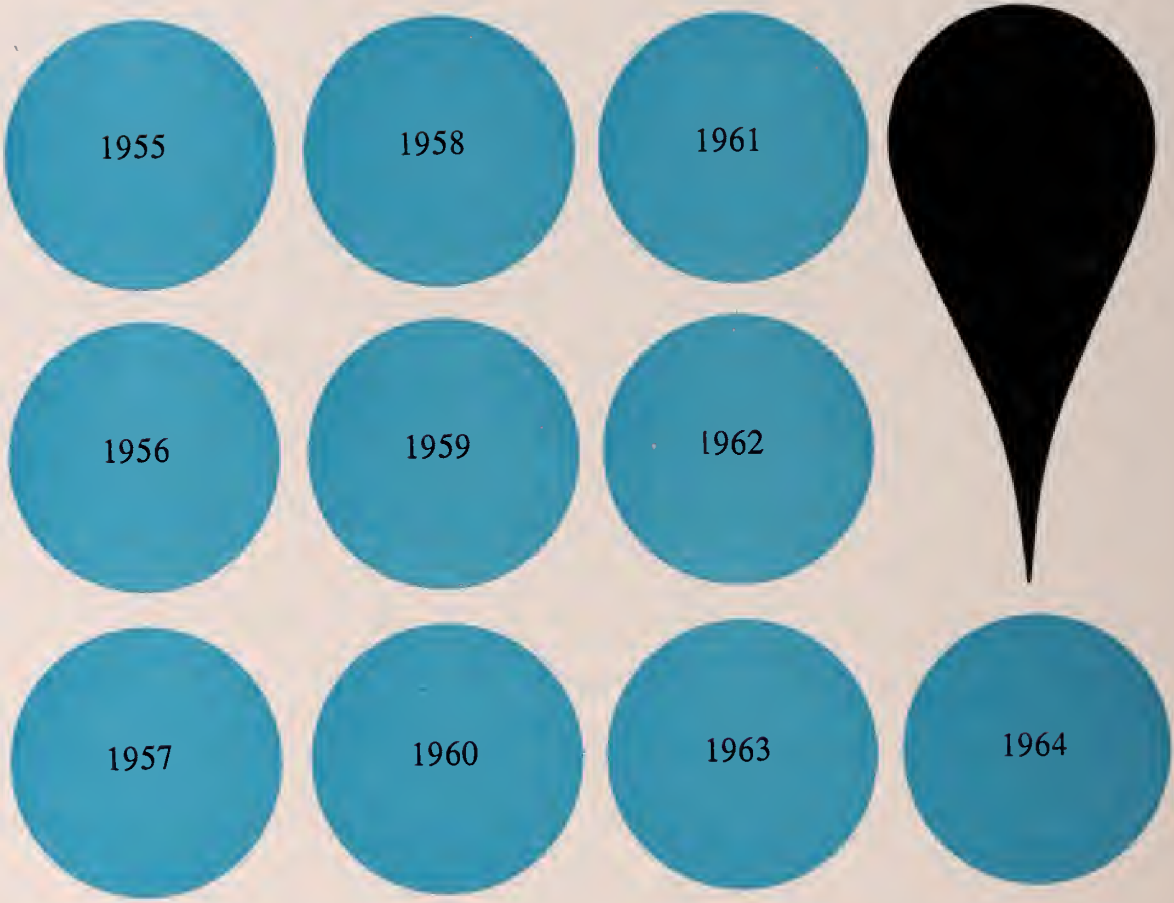
The
clear
conclusion
from
10 years'
experience...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is profoundly affected or acute manifestations of a grave nature supervene. Long-term management of several patients by Brunsting (1954) showed a general improvement and some recovery of hepatic function. In Turkish porphyria the lesions of the skin improved shortly after hospital admission and some facial clearing of the hyperpigmentation was noted, although the massive excretion of porphyrin remained unchanged.

Some Diagnostic Considerations of the Forms of Porphyria Hepatica

Acute Abdominal

A differential diagnosis would have to cover all acute abdominal conditions, psychosis and psychoneurosis, and disease of the nervous system. The diagnostic possibility should be present in the clinician's mind when he is facing a patient with numerous surgical scars and history of recurrence of abdominal pain. Patients with porphyria very often have laporotomies when presenting the picture of an acute abdomen. Naturally, omission of the Watson-Schwartz test in the presence of abdominal tenderness, vomiting and constipation with no clear cut etiology would be inexcusable.

Dark Urine

The diagnosis of acute porphyria is sometimes wrongly made in other conditions in which patients present dark red or dark brown urine: for example, in alkaptonuria, idiopathic myoglobinuria, severe lead poisoning, or the preicteric phase of infectious hepatitis when the urine contains much urobilinogen.

Photosensitivity

The manifestations of the two varieties of porphyria cutanea tarda, being similar dermatologically speaking, can be discussed together if we keep in mind the primary hepatic disease in porphyria cutanea tarda symptomatica. The most important group of skin diseases from which to differentiate the cutaneous hepatic porphyria is light-sensitivity dermatitis due to other photosensitizing substances in which porphyrin metabolism is normal, subacute disseminated lupus erythematosus, dermatomyositis, epidermolysis bullosa; all of these must be taken into consideration. The lesions of epidermolysis bullosa, as of cutaneous hepatic porphyria, are precipitated by trauma, but the sites affected are those exposed to pressure and friction, not necessarily those exposed to light as in porphyria. There have been reports in which the lesions have simulated dermatitis factitia, impetigo, acne necrotica, and xeroderma pigmentosum. In some cases the violaceous plethoria and hirsute facial appearance suggest Cushing's syndrome. Sometimes the hyperpigmentation is suggestive of Addison's disease or hemochromatosis.

The onset of symptoms, usually between the ages of 10 and 30 years, and the increased excretion of coproporphyrin and protoporphyrin in the feces at all times will establish the diagnosis of porphyria cutanea tarda hereditaria. In porphyria cutanea tarda symptomatica the primary liver disease and the absence of increased porphyrin in the feces are constant features.

Numerous cases of porphyria hepatica have been reported in which skin lesions and the classical manifestations of acute intermittent porphyria coexist in lesser or greater degree. For that reason, some authors have made

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different classifications, grouping these cases under denominations of porphyria mixta and porphyria variegata. It is doubtful that any classification of porphyria at this time is definite. It will suffice for the clinician to know that in porphyria, as in any disease, the divisions are artificial. The clinical picture may lie anywhere between acute intermittent porphyria and porphyria cutanea.

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11-21 can be obtained from Grand Rounds Editor at Mt. Sinai Hospital.

Roger Bacon 1214(?)-1294

To Roger Bacon goes recognition for his optical studies on the structure of the eye, on perspective and light, and on magnification through lenses. He was not a doctor; he was a Franciscan friar absorbed in medicine and well-read in the works of Hippocrates, Galen, and others — despite the Church's edict against any interest in science, including medical science.

Bacon maintained that we have three means of knowledge: first, authority, which forces opinions on the mind without instructing it; second, reasoning, which can theorize but not substantiate; and third, experience, which alone can establish and verify.

For his forthright convictions and the courageous expression of them, Bacon spent long years under persecution and in prison. Only an enlightened posterity extended long overdue recognition to a brilliant pioneer in the field of optics.

The most utterly lost of all days is the one in which you have not once laughed.
—Kasco Informant

Industrial Medicine

The Preplacement Examination

Many physicians perform preplacement examinations which may vary all the way from those for high safety-requirement jobs with rigid standards set by law and deemed necessary to protect the public to those for small industries where no standards are set. Moral, legal, and economic reasons justify these examinations as an aid in selecting employees who have emotional stamina and physical capacity for the work under consideration. More often than physical disability, unfavorable adaptation is due to lack of skill, poor motivation, or the inability to get along with fellow-workers. In spite of this, properly selected employees who are healthy and kept healthy are productive employees. Physical examinations are of importance in that they focus the attention of the employees on the emphasis which management places on good health.

Such a program must not follow rigid lines but should be flexible and subject to change. The value of the examination is enhanced by an understanding physician who inspires confidence and indicates concern for the employee. Under these conditions it can serve as a valuable tool in case finding, and with proper counsel the examinee can be returned to the care of his private physician.

The preplacement examination should be required as a condition of employment prior to hiring, and can later serve as a baseline evaluation to determine subsequent disability in event of claims. The report of the examination should be returned to management with a concise statement of employability, noting any limitations placed thereon, but without privileged diagnostic information.

Small businesses (less than 500 employees), which employ 75% of workers in the labor force, often have no medical department and no set of physical standards for employment. Usually the physician, employed on a part time basis, works with the personnel division. The question then arises as to what the physical requirements for employment should be? In selecting physical standards, allowance must be made for human concern, the need for employees with desired skills, and the fact that selection of a good employee is not made entirely on a physical basis. The examiner must tour plant facilities periodically and become aware of work environment in order to establish the criteria for employability on the basis of experience and the management's philosophy. These criteria must not be arbitrary and based on medical opinion alone. With the above points in mind the examiner should formulate a program to follow.

First, a brief history should be taken to elicit important facts bearing on the health of the examinee. Histories recorded by a clerk are of some value; but frequently those seeking employment will be reluctant to admit a history of many defects on this routine type of questioning. Such a history should therefore be supplemented by skilled interrogation by the examiner as he is performing the examination. In certain hazardous occupations it might be well to follow specific lines of questioning and make a note of denial of defects.

With these ideas in mind an attempt will be made to give some general guide lines to serve as standards for employability. Uncorrected vision of 20/200 or better in both eyes is acceptable for many kinds of work if correctable to 20/30 in one eye and 20/40 in the other. Where one eye is blind or defective (20/200 or less with or without glasses), the prospective employee should be rejected for employment on machines where eye injury may result. Hearing may be tested with spoken or whispered voice except in situations where noise is a hazard; then audiometric

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studies should be done before exposure to establish base-line hearing ability, with later studies made periodically as indicated.

Acute illness and disqualifying correctable defects (e.g., herniae) are cause for rejection subject to re-examination after recovery or correction. Heart disease of a severe nature with decompensation, angina, endocarditis, myocarditis, and uncontrolled hypertension, are usually cause for rejection. A chest X ray should be part of the examination to exclude the possibility of exposing employees to contagious disease. Respiratory disease reducing vital capacity below a functional level is cause for rejection, also malignant disease, unless the examiner can be satisfied that it has been cured. Orthopedic defects must be evaluated on the basis of function for the type of work under consideration. A urinalysis should be performed to exclude uncontrolled diabetes and advanced kidney disease.

In conclusion, the outline presented above is broad in nature and must be interpreted by each examiner. Every person examined gains some impression of the medical profession as a whole; and we should make every effort that this impression be a good one. Rejected examinees are usually satisfied if we take time to point out in a friendly manner why they were disqualified, and if possible to show them that the job sought might only aggravate their defects.

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ASTROLOGY AND MEDICINE

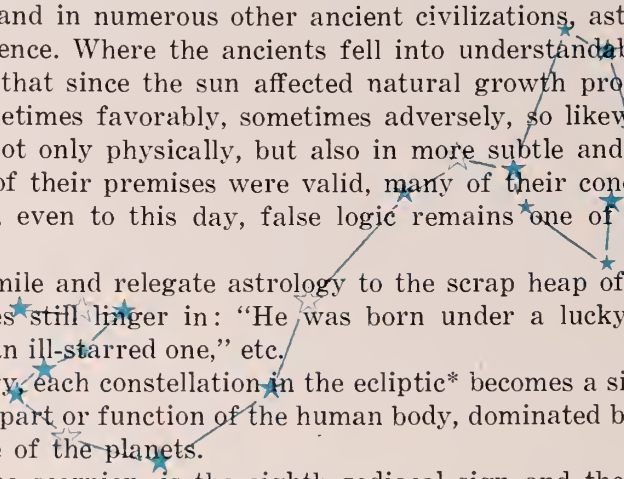
Scorpio

"The man who is ignorant of the science of astrology, deserves the name of fool rather than that of physician." — Hippocrates

In Greece and in numerous other ancient civilizations, astrology was a reputable science. Where the ancients fell into understandable error was in assuming that since the sun affected natural growth processes on the earth — sometimes favorably, sometimes adversely, so likewise was man affected — not only physically, but also in more subtle and occult ways. While some of their premises were valid, many of their conclusions were fallacious as, even to this day, false logic remains one of man's major pitfalls.

We now smile and relegate astrology to the scrap heap of superstition, but its echoes still linger in: "He was born under a lucky star," "The voyage was an ill-starred one," etc.

In astrology, each constellation in the ecliptic* becomes a sign indicating a designated part or function of the human body, dominated by the sun, the moon, or one of the planets.



Scorpio, the scorpion, is the eighth zodiacal sign and the constellation occupied by the sun from approximately October 22 to November 22, and therefore not visible at that time. Astrologically, it is a powerful and compelling sign governing the generative organs, the bladder, the pelvis, and also the ureters and urethra.

Some of the diseases peculiar to natives of this sign, so unfortunate as to have adverse planetary influences militating against their health, would be pathologies of the generative system, venereal disease, hemorrhoids, fistulas, prostate trouble, and urethral stricture.

For anyone intrigued by astrological myth, Scorpio is a spectacular constellation that can be seen almost directly south during July evenings, and is easily identifiable because of its cat's eyes, and its heart, the red star Antares, one of the few red stars visible to the naked eye. Because of its color it can be confused with the planet Mars which from time to time invades this constellation.

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*Apparent path of the sun as seen from the earth.

Abstracts, Briefs and Commentaries

HIATUS HERNIA

A review of 600 hiatus hernias at the Leahy Clinic by Crozier and Jonasson, as disclosed by X-ray examination, indicates that approximately only 18% present clinical symptoms unassociated with other gastrointestinal diseases. The most commonly observed symptoms attributable to the hiatus hernia were regurgitation of gastric contents while in a recumbent position, bleeding as a result of esophagitis or esophageal ulcer, cough, choking, wheezing only when in a recumbent position, and coronary-like or angina-like symptoms. Food distress, dysphasia, and bleeding were also observed. The problem of overweight was no greater than that which is observed in the general population of the same age group.

Approximately 82% of the cases of hiatus hernia were found in the course of investigating symptoms of constipation, belching, bloating, flatulence, or other nonspecific symptoms referable to the gastrointestinal tract.

These authors found that approximately 53% of the patients obtained satisfactory benefit from medical management, using ulcer-type diets and recommending that the larger share of the caloric intake be consumed the earlier part of the day, leaving only a small meal for the evening. They also recommended the suppression of belching and the elimination of bedtime eating.

Surgery was resorted to in those cases suffering from bleeding, stricture, ulcer, or symptoms of incarceration.

It is well to keep in mind that the mere finding of a hiatus hernia by X ray does not necessarily indicate that this condition is the cause of a patient's symptoms. The high incidence of benefit by medical management offers a reasonably satisfactory clinical trial when coexisting disease may confuse the diagnostic picture.

Carl O. Rice, M.D.
Minneapolis, Minnesota

Crozier, Robert E. Jonasson, Hauker: Symptomatic Esophageal Hiatus Hernia. Arch Int Med 113:737, 1964.

VENOUS PERFORATION DUE TO POLYETHYLENE CATHETER

The author cites a case of perforation of innominate vein secondary to seven days of inlying venous catheter, size 200, for purposes of intravenous feeding.

The patient developed swelling and ecchymosis and subcutaneous emphysema. The leak was proven by venogram and recovery rapidly followed removal of the tube.

The author suggests that this complication can be averted by withdrawing the catheter a short distance prior to fixation to the skin, and is of the opinion that perforation occurs due to pressure necrosis at the tip of the catheter against the vein wall.

Inlying venous catheter for intravenous alimentation has obvious advantages over multiple needle punctures, particularly in people with difficult veins. However, these are, as in this case, several complications that do occur and the physician must be alerted to these possibilities. Although it is advisable to have the catheter up into as large as vein as possible, it likely is inadvisable to go as far as the innominate, since perforation and extravasation are not at all uncommon. Such a problem is obviously more evident and less serious if the extravasation occurs outside the chest cavity. The author suggests withdrawing the catheter a short distance and this seems wise. However, it is important not to withdraw the catheter against a sharp needle, since the tube may easily be cut off by this maneuver and embolization of the catheter may well follow. One could suggest that the needle employed for insertion be withdrawn from the skin before withdrawing the catheter prior to fixation.

J. H. Strickler, M.D.
Minneapolis, Minn.

Ashraf, M. N.: Venous Perforation Due to Polyethylene Catheter. Ann Surg 157:375, 1963.

UMBILICAL HERNIAS IN SMALL CHILDREN

The authors review various reported series which document the spontaneous disappearance of the great majority of umbilical hernias in infancy and childhood. Since the mechanism of closure has not been studied the authors decided to measure the umbilical rings and hernias in such children up to the time of disappearance.

On the basis of serial caliper measurements the area and volume of the umbilical hernia were calculated for seventy-eight patients. The hernias disappeared in seventy-two instances. The remaining six were still present at time of completion of the study. Excluded from the study were hernias less than 0.5 cm. in diameter. Forty per cent of the hernias disappeared in the first year of life.

Two patterns of ring contracture were observed. Approximately one third underwent gradual logarithmic reduction of the area of the ring. In most of the others the ring remained unchanged for an indeterminate time and then underwent the same gradual reduction. Some actually enlarged in the first month. In nearly all instances obliteration occurred within a year from onset of decrease in size. The average decrease in the ring area was 18 per cent per month.

It was often observed that reduction in hernia volume did not parallel reduction in ring size. Some hernias remained unchanged until just before closure of the ring. Some became smaller during the last month or two of ring reduction. It was felt that a delaying factor in some instances was the presence of diastasis recti.

The authors conclude that their observations confirm other impressions that infantile umbilical hernias almost invariably close spontaneously. Measurement data show the closure to be due to centripetal contraction of the fascial edges of the ring. In their opinion strangulation is the only indication for operative closure of umbilical hernias in infants and children.

The study reported is a rather unique investigation of a commonplace but very practical problem. The propriety of observation as the sole therapy for umbilical hernias in this age group bears repetition. On the contrary, in the adult, where an umbilical hernia may constitute more of a potential danger, the factors of growth and development are absent and operative correction is in order.

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Minneapolis, Minn.

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PULMONARY EMBOLISM

This is an excellent monograph of the causes, prevention, and treatment of pulmonary embolism. The bibliography contains 132 reports. The authors review the subject quite well in an easily read report. The subject is current, the treatment is changing, and I believe that the monograph, although too lengthy to describe in detail, should be read by all physicians.

Jerome T. Grismer, M.D.
Minneapolis, Minn.

Beall, A. P. C., Jr., Fred, H. L. and Coole, D. A.: Pulmonary Embolism. Curr Probl Surg 2:1964.

ACUTE SODIUM DEPLETION IN NORMAL AND ALCOHOLIC MAN

Acute sodium depletion in five normal adults produced weakness, hypometabolism and apathy. In five alcoholics it resulted in motor agitation and delirium with increased metabolism. The alcoholics were all chronic and had experienced delirium tremens at least once, but had not drunk alcohol for three or more months before the experiments. They looked healthy and felt well prior to the depletion. Both groups promptly regained normality with repletion. Other measured biological effects were the same in both groups.

The sodium depletion was produced by suction removal of the contents of the second portion of the duodenum with intravenous administration of 5% dextrose as replacement. The depletion was progressive until serious hypotension, profound weakness or oliguria appeared, when restitution was accomplished by substitution of Hartmann's solution for the dextrose.

Oxygen consumption, body weight, hematocrit, serum chloride, sodium, biocarbonate and potassium were determined daily. Urinary sodium, duodenal fluid sodium, potassium and chloride were determined every six

Continued

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hours. Blood pressure, pulse rate, reflex muscle activity, temperature and mental status were determined every four hours. From this data the mEq. of Na/Kilogram loss could be calculated and correlated with the biological responses.

These studies showed that in non alcholics physical and mental apathy appears with removal of 1 to 4 mEq/Na per kilogram. Physical and mental incapacity and partial renal failure occur with 4 to 8 mEq/Kg loss. Circulatory shock and renal failure appear with 8 to 14 mEq/Kg deficit, and death follows loss of more than 14 mEq/Kg.

It is significant that shock levels of sodium depletion were produced in perfectly normal adults by only two to three days of duodenal suction accompanied by water repletion, using 5% dextrose. The failure of either serum Na or urinary Na determinations to reliably reflect the magnitude of Na depletion in these acute studies indicates that these determinations cannot be relied upon in similar clinical cases.

The best reflection of the quantity of Na in the body was found to be plasma volume. Thus with acute progressive Na loss the hematocrit rose proportionately, and in this study the only reliable determination indicating the magnitude of Na loss was the hematocrit. (Other more reliable methods of determination of plasma volume would be even more valuable in acute situations complicated by both blood loss and Na deficit.)

The surgical, medical and psychiatric implications of this study are tremendous. First, the reduction of oxygen consumption in the normal human by 40% with acute Na depletion indicates that healing of wounds, detoxification of drugs and metabolites and cerebral physiology are grossly impaired, even though shock may not yet be apparent. Secondly, the increased psychomotor activity and oxygen consumption in the alcoholic, even though three to six months dry, illuminate the recognized propensity of alcoholics to develop delirium with injury or toxicity. From these studies it is quite understandable why a bout of anorexia with vomiting precipitates delirium tremens in the alcoholic. Finally, what other preconditions, besides alcoholism, may grossly alter the biological response of the organism to disturbances in the internal environment, and what hazard does the extensive use of saluretic diuretics constitute for the alcoholic, or the victim of acute intestinal malfunction or severe bodily injury or burn? The patient with body Na already depleted to the point that serum volume is reduced (the goal of diuresis for either heart failure or hypertension) is some trouble before trouble begins.

In these days of increasingly esoteric surgical manipulations of more and more unlikely animals for the gaining of bits of knowledge of doubtful application, it's reassuring to find a study by a professor of surgery conducted on human beings. Well planned and executed studies of humans are often quite valuable. Carl Moyer and his colleagues are to be congratulated on this splendid work.

N. Kenneth Jensen, M.D.
Minneapolis, Minn.

Grayson, Ted L., White, Jacob E., and Moyer, Carl A.: Oxygen Consumptions; Concentrations of Inorganic Ions in Urine, Serum and Duodenal Fluid, Hematocrits, Urinary Excretions; Pulse Rates and Blood Pressure During Duodenal Depletions of Sodium Salts in Normal and Alcoholic Man. Ann Surg 158:5, 1963.

MYELOFIBROSIS

Reported are twelve cases of myelofibrosis among patients who came to necropsy at the atomic bomb casualty commission, Hiroshima, Japan. Of the twelve patients, nine were exposed to a significant amount of ionizing radiation at the time of the atomic bomb explosion on August 6, 1945. The authors express the view that the frequency of myelofibrosis among exposed persons varied inversely with the distance from the hypocenter at the time of the explosion. The patients were selected from those recorded as demonstrating extramedullary hematopoiesis and significant unexplained bone-marrow fibrosis, or unexplained splenomegaly, or combinations of these, for the period 1950 to 1959. The diagnosis was made from examination of the blood smear and review of necropsy tissue. Patients known to have received X ray or radiophosphorus treatment were excluded. Four of the patients had leukocyte counts of 183,000 or more per cubic millimeter and only four had leukocyte counts of normal or less than normal. Eight had moderately to maximally increased myelopoiesis in the bone marrow. In only two was myelopoiesis assessed at less than normal. Megakaryocytopoiesis was normal to increased in all marrows, whereas erythrogenesis was increased moderately or markedly in only three marrows, was increased slightly in five, and was decreased in three. The pathogenesis of myelofibrosis is discussed and the authors' consideration of the interrelationships of "myeloproliferative disorders" is outlined. The authors express the belief that there is little evidence in the study presented to support the concept that myelofibrosis represents a primary bone-marrow failure with secondary compensatory hematopoiesis. They take the view that there is no evidence to support the concept that myelofibrosis might be secondary to another "spent" hematologic disorder. The peak incidence occurred within ten years after explosion of the atomic bomb, at about the same time that leukemia reached it peak, and before any patients with polycythemia or erythroleukemia came to necropsy. They also state that no cases of myelofibrosis have been recorded in necropsies in the period subsequent to the present study. The role of tuberculosis in the genesis of myelofibrosis is discussed, as three of the twelve patients presented had tuberculosis, but it is not thought that tuberculosis was the cause of myelofibrosis in these patients. The authors conclude: "Although the present report strongly implicates ionizing radiation in the development of at least some cases of myelofibrosis, it does not exclude the possibility of other or even synergistic agents."

Edwin D. Bayrd, M.D.
Rochester, Minn.

Anderson, Robert E., Hoshino, Takashi, and Yamamoto, Tsutomu: Myelofibrosis With Myeloid Metaplasia in Survivors of the Atomic Bomb in Hiroshima. Ann Int Med 60:1, 1964.

FROSTBITE

Frostbites cause many casualties in fighting armies. Those of the Russian expedition of Napoleon's army have been reviewed.

In Finland, 200 cases of frostbite injuries are severe enough to demand hospitalization annually. Between 1939 and 1956 246 deaths occurred directly or indirectly from cold exposure, i.e., 15 cases a year. Between December and January, 1939 and 1940, there were 5,602 cases of frostbite in the Finnish army. It was estimated that 12 percent of 66,000 troops had frostbite during the winter war. The number of cold injuries in the Russian army was reported as being 8.12 percent of all cases requiring medical treatment. In World War I, 115,361 men in the British army suffered from cold injuries. In World War II, 55,331 soldiers of the United States army received cold injuries, the majority occurring at the European front in the winter of 1944-1945. The German army, during the Russian expedition, 1944 and 1945, suffered approximately 979 cold injuries daily.

Incidence

Frostbite cold injuries were most often in the extremities: 67 to 88 percent in the lower extremities, 10 to 21 percent in the upper extremities. One and one-half percent involved the ears. The cause of frostbite was considered to be clothing which was too tight, especially boots. Wet feet was a frequent factor.

Causative Factors

In the British army, trench foot was a result of cold, moisture, and lack of activity among soldiers in shell holes. Leather boots and mittens, with two pair of wool socks, were often inadequate, and the inability to change to dry socks often continued throughout the whole period of front line duty. In some instances there was sensitivity to cold, malnutrition, fatigue, the hanging position of the feet, ill health, circulatory disease, infection, scars, and earlier frostbite.

It was felt that tobacco had no effect on the incidence of frostbite but that alcohol proved to be productive of injury, especially when there was intoxication, so that unnecessary exposure resulted.

Pathology

As a result of circulatory disturbance experimentally, vasoconstriction and stasis occur before actual freezing. The small arteries are found to be full of a fine-grained colorless mass.

Killian observed (1) that all peripheral arteries, arterioles, and capillaries contract. (2) This is followed by strong dilatation of capillaries and quick flow of blood. (3) Dilatation in capillaries continues and circulation decreases; stasis occurs in the capillaries, in venous plexus, and in venols, while a persistent spasm takes place in the pre-arterioles and in arteries. In larger veins maximal dilatation, agglutination, and thrombosis occur. (4) At the healing stage reactive hyperemia of different degrees occurs.

Light cold exposure led to arterial spasm and increased permeability of vessel walls. Severe cold causes complete cessation of circulation during exposure. There is a growing need and lack of oxygen in the tissues. The site of stasis may become necrotic. The necrosis of tissue is initially caused by partial or complete cessation of circulation. Cell death takes place before the freezing of tissue liquid.

Factors Influencing Freezing

The degree of freezing was influenced to a large extent by: (1) the air temperature and (2) the length of exposure.

Most of the cold damage was produced when the temperature ranged from −15 degrees centigrade to −40 degrees centigrade. The duration of exposure of those with cold damage ranged from short periods to 14 days.

Continued

The mean point of exposure was 37.5 hours. In a group of civilians, 47 percent were lumbermen who were working in the woods.

Treatment

The interval between exposure and treatment was directly comparable to the duration of recovery. In the treatment of cold injuries the usual forms of treatment were employed. Sympathectomy was done on 38 patients with good results in 17 cases. Sixteen presented satisfactory results and poor results were evident in five cases. The most favorable results were in patients who suffered peripheral vascular disease. Those who received care within two hours had the quickest healing period.

In surgical instances in which necrosis occurred, best results were obtained when a line of demarcation was established.

Abstractor's note: This 69-page report of a review of the literature indicates that the temperature of the air and the duration of the exposure were dominant factors in tissue damage and in the end results. Many other factors, such as fatigue, malnutrition, clothing, peripheral vascular disease, and the degree of tissue damage were factors in influencing complications and sequelae. Dry treatment was generally considered to be the best. Antibiotics were helpful in infected cases. Anticoagulants were of doubtful value. Sympathectomy was worthwhile in properly selected cases.

After reading this tremendous publication, one must be impressed with the many advances which have been suggested for hunters, explorers, skiiers, and outdoor laborers — insulated boots, quilted underwear, face masks, helmets, hand warmers. The author is to be congratulated on this extensive exposition.

Stanley R. Maxeiner, Sr.
Minneapolis, Minn.

Eero Ervasti: Frostbites of the Extremities and Their Sequellae—A Clinical Study. Acta Chir Scand Supplementum 299.

COLLES' FRACTURE

The difficulties of treating Colles' fracture are insufficiently recognized. As other writers have also pointed out, serious permanent disability too often remains. This paper studies the factors which underlie successful treatment. Colles' fractures were examined in 210 cases one to seven years after injury, nearly all treated by recently graduated doctors. Assessment included numerical estimates of movement and power as well as the patient's own opinion of efficiency and appearance, using the opposite wrist as the standard for comparison. In the first series (110) many methods were used; in the second (84), a unified scheme of reduction with an above elbow cast, which was worn for four weeks. The latter series showed appreciably better over-all results. Neither age nor severity of the fracture much influenced the results, but radio-ulnar luxation was found to be a cause of serious disability. Both series showed clearly that the better the reduction of deformity seen in the final X rays, the better was the function of the wrist and hand.

Courtesy of References and Reviews
Journal of the American Medical Association

Golden, G.: Lancet 1:511, 1963.

A detour may be best, unless you can meet the requirements of a tough, uphill climb.—Harvard Business Review

Book Reviews

A book may be compared to your neighbor; if it be good, it cannot last too long; if bad, you cannot get rid of it too early.—Brooke.

CLINICAL DISORDERS OF THE HEART BEAT — Dr. Samuel Bellet, M.D., Lea & Febiger, Philadelphia, 1963. Second edition, 1074 pages, price $28.00.

It is Dr. Bellet's intent to discuss in detail the various "Clinical Disorders of the Heart Beat." That he has succeeded is attested to by the fact that Sinus Irregularities are discussed in twenty-one pages or perhaps that Premature Beats are dealt with in sixty-two pages.

After comprehensive discussions of the various arrhythmias, a sizable portion of the book discusses the arrhythmias found in certain clinical states. One might not expect to read about the arrhythmias associated with pregnancy, arrhythmias of the fetus, or those seen in schistosomiasis, typhus, acromegaly, or hemochromatosis, but these and many other entities are discussed.

Therapeutic agents are discussed twice, first in a section dealing with the specific arrhythmias and again individually in a section devoted to drug therapy. It is hard to think of a drug or type of therapy that is left out.

A glossary is attached where one can find defined such unlikely terms as Accrochage, the Carey-Coombs murmur, Bahnung, and the Dip phenomena. One may also read that trigeminy is a condition in which two premature beats follow each normal beat.

The timely subject of cardioversion is well discussed, and a very reasonable position regarding the present indications for this procedure is taken.

In summary, this book would be a helpful one to have available in a hospital library or perhaps as a reference work for the full or part-time cardiologist. It is truly amazing that a book can contain so much information with so few obvious errors. At the same time, the encyclopedic nature of the book would tend to discourage its being used other than as a reference work.

Alan P. Rusterholz, M.D.
St. Paul, Minnesota

CLINICAL INVESTIGATION IN MEDICINE: LEGAL, ETHICAL AND MORAL ASPECTS. AN ANTHOLOGY AND BIBLIOGRAPHY — Ed. by Irving Ladimer and Roger W. Newman; Boston University Law-Medicine Research Institute

This is an anthology and bibliography prepared by the Law-Medicine Research Institute of Boston University; the publication was aided by a grant from the Schering Foundation, Inc. This 517-page paperback book is an informative volume and represents a useful reference work.

The anthology section of the volume (seven chapters) contains 73 selections from the available literature; many aspects of clinical investigation are discussed. The selection of topics is very satisfactory. The material presented has been selected from medical journals and also from the publications of a great many other disciplines. The chapter on Scientific Design and Technique is a particularly informative one. The following quotation from Mindel C. Shep's 1962 paper (Problems in Clinical Evaluation of Drug Therapy) is indicative of the importance of this general problem to clinicians: "The practicing physician faces a dilemma. He is often subjected to conflicting claims without evidence from acceptable clinical evaluations sufficient for a reasonable choice. Furthermore, his education has not always instilled that critical approach to evaluating therapy which is needed now even as in the days of blood-letting." Shep comments on the fallacy of crediting clinical improvement to a given drug when it may have been related to some other concomitant factor. Our problems are not new; in 1689 Gideon Harvey published a book, "The Art of Curing Diseases by Expectation." It is well, in 1964, to be reminded of the pitfalls that beset all investigators engaged in clinical drug trials.

This anthology and bibliography can be recommended as an informative volume.

F. W. Hoffbauer, M.D.
Minneapolis, Minnesota

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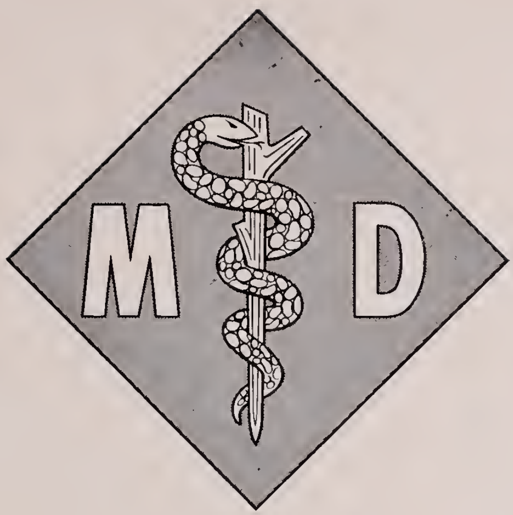

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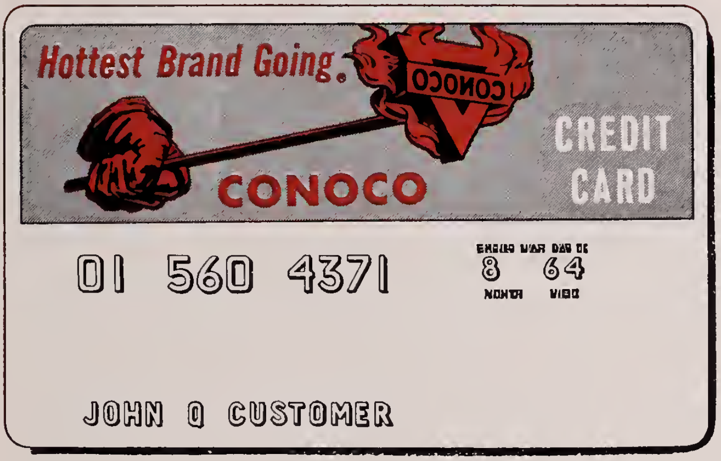

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Perinatal Mortality Study

Fetal and Neonatal Deaths

Committee Report for 1962

During the past two decades, great strides have been made in reducing maternal mortality. Paradoxically, however, in a state noted for excellent medicine, we are following the general trend of the country as a whole in our failure to reduce infant mortality.

The Hennepin County Perinatal Mortality Study Committee is keenly aware of this problem and after the eleventh year of study of all perinatal deaths, feels strongly that something additional must be done. In each year of study, the committee has identified preventable factors in numerous infant and fetal deaths, but there has not been an effective dissemination and application of this information either in Minnesota or elsewhere.

Our country has dropped to eleventh place among twelve countries, using the World Health Organization analyses. It is incredible that a state so medically sophisticated as ours should have an average higher neonatal mortality than Australia, New Zealand, or Denmark, for example.

Our poor record in reducing preventable factors indicates an urgent need for more comprehensive perinatal studies, broader dissemination of information gained, and greater practical application of this data to correct conditions that result in unnecessary fetal and neonatal loss.

The multiple problems involving premature labor, fetal anoxia, resuscitation of the newborn, neonatal hemorrhage, erythroblastosis, infection, medication effect, and placental and cord pathologic physiology have a causal relationship with perinatal morbidity, which is probably at least tenfold the perinatal mortality. Much study in this area is still necessary to adequately assess the present status of therapeutics.

The Hennepin County Perinatal Mortality Study Committee has completed 11 years of study of fetal and neonatal deaths occurring within the County. Studies include all neonatal deaths in the first 28 days of life and all fetal deaths of 20 or more weeks gestation. Approximately 10 per cent of all cases studied exhibit preventable factors. This is comparable to findings in similar studies throughout the country.

Incidence

Table 1 indicates that there were 24,624 live births with 292 fetal deaths (over 20 weeks gestation) in Hennepin County in 1962. In addition, there were 395 neonatal deaths (during the first 28 days of life).

Continued

TABLE I
Live Births, Fetal and Neonatal Deaths by Place of Occurrence
(Hennepin County), 1962[1]

Place of Occurrence	Live Births	Fetal Deaths*	Neonatal Deaths**
Hennepin County, Excl. of:	4,964	57	70
Minneapolis	19,660	235	325
TOTAL	24,624	292	395

*Over 20 weeks gestation
**During the first 28 days of life
[1] Minnesota Vital Statistics, 1962. Minnesota Department of Health. 72pp.

Preventable Factors

The committee received and reviewed 150 fetal deaths and 125 neonatal deaths, approximately 40 per cent of the 687 fetal and neonatal deaths occurring in the county in 1962.

Preventable factors were identified in 27 (10%) of the 275 cases reviewed by the committee. If all cases had been reported to the committee, it is probable that another 40 cases might have been assigned preventable factors. This data illustrates the continuing need for the welfare of the unborn and the newborn.

Inadequate Prenatal Care

This problem seemingly is greater in certain socioeconomic groups. Approximately 22% of mothers delivered at the local General Hospital had made no prenatal visits and another 22% had made only one prenatal visit prior to admission for delivery. Public health aspects of the problem must be considered. Hospital evaluation of patients with little or no prenatal care must be thorough. It seems obvious that more strict applications of the accepted minimal standards of prenatal care by family, physician, and hospital are necessary. One patient with active tuberculosis, one active leutic, and two diabetics were among those studied who had had no prenatal care. These findings reiterate the need for laboratory screening of all patients for these entities during the prenatal period.

Rh determinations are still not being made on all prenatal patients, and some physicians are not testing Rh negative mothers for antibody titers.

Self-induced premature labor and failure to report membrane rupture are other factors in this category.

Another problem which perennially recurs is inadequate evaluation of fetal size prior to elective Cesarean section. Emergency Cesarean sections are not considered in this evaluation. The use of X ray to aid in diagnosis of maturity greatly decreases the chance of a gross error.

Second Stage of Labor

The onset of fetal distress in labor is often unrecognized by attending personnel. In the second stage of labor only adequate recognition of fetal distress will allow proper therapy to be instituted. In busy delivery suites, it appears that fetal heart tones are not auscultated as often as necessary for the baby's welfare. Review of second-stage losses fails to reveal timing of auscultation. It must never be assumed that the fetus is safe because the mother is in the delivery room. Development of a simple efficient monitor for fetal heart tones will help this problem; but in the meantime, frequent auscultation in labor and especially during the second stage will alert the physician to correct some of the losses which have no other explanation than distress in labor.

Injudicious Pitocin

The injudicious usage of pitocin again "rears its ugly head" too frequently in most perinatal studies. Adherence to the suggestions outlined by the American College of Obstetrics-Gynecology are helpful, but this is primarily concerned with inductions. A copy of the Suggested Guide for Obstetric Hospital Practice prepared by the Minnesota Maternal Health Committee is available in all hospitals. Use of pitocin in breech presentations must be carefully considered only by a skilled operator. One case was studied in which the use of pitocin was associated with development of a contraction ring over the aftercoming head and a fetal death resulted during the second stage.

The relatively recent recognition of incompetent cervical os and its successful correction has been an aid to many who have had "poor OB history." The speculum and bimanual examination of the pelvis during pregnancy is no longer considered "poor medicine." The problem goes unrecognized if no examinations are made. One such case was reviewed by the committee and considered a preventable factor.

Premature Labor

Premature labor is still not well understood, but adequate and prompt therapy may give an extra few days or weeks of extra maturity that so often make the difference between fetal survival and demise.

In two cases, the use of delayed or nonusage of chest X ray in newborns with respiratory distress was scrutinized. In one case, the baby lived 54 hours with no chest X ray being ordered to evaluate respiratory distress. Two cases were found to have diaphragmatic hernia on the post-mortem examinations, both infants living a variable number of hours. Recent case reports in the Hennepin County Bulletin and in Minnesota Medicine detail this problem. The committee has long felt a need for a study in depth of certain categories of fetal loss. It is felt that this would aid in pointing out preventable factors and in making specific recommendations on the same basis that the maternal mortality committee studies have resulted in a brochure, "Suggested Guide for Obstetric Hospital Practice."

Conclusions

The preventable factors actually identified in our studies put into sharp focus the fact that preventable perinatal deaths do occur in our community. It is the earnest hope of this committee that the members of the medical profession will lend all possible support to any other committee assigned to gather the data essential to an understanding of the nature of the problem that will help achieve methods of correction.

The following points are made by the committee as generally indicative of the aims of studies now in progress and are based on findings indicating definite needs in these areas.

1. Encourage conventional rather than unorthodox management of obstetric and pediatric problems.

Continued

2. Encourage more prompt and frequent usage of chest X ray of the newborn.

3. Encourage closer watchfulness of fetal welfare in the second stage of labor. Further development of a practical, inexpensive fetal heart monitor is almost certain, because the need is great.

4. Encourage freer use of consultation in OB and pediatric areas.

5. Encourage frequent reassessment of our own methods of practice to be certain we are not omitting any details, and to bring our methods up to date to conform with all new and proven advancements in care and therapy.

6. Encourage all physicians to join us in our desire to understand why our state's neonatal mortality rates are high in comparison to certain other countries and to help find a way to "lead the world" in this area.

Wigs and Medicine

"For several hundred years, starting with the sixteenth century, wigs were part of the adornment of all men in the fashion. There is every reason to believe that wigs and court plaster owed their vogue to a medical complication — the fifteenth- and sixteenth-century epidemic of syphilis that wrought such havoc with the courtiers. The baldness resulting from this disease necessitated a resort to wigs, and the facial blemishes led to the invention of court plaster — used, as its name implies, first in the courts.

"Even when there was no longer the need for wigs, the vogue continued because their advantage had been discovered in the control of another medical complication — a dermatological one — head lice. So far as one can tell, these parasites were, in bygone days, of almost universal occurrence among rich and poor alike. As you read Pepys' diary, note the unconcern with which he records the fact that his wife in looking through his hair, found twenty, both great and small. He was thinking at the moment of buying a wig. And note also his comment on his bed at an inn, 'good but lousy — which did make us merry.' "*

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*Haggard, Howard W., M.D.: "The Lame, the Halt, and the Blind," p. 19.

The Prey of Fear

Men are as apt as women to allow their imaginations to run rampant. A man retired and hardly knew what to do with himself. As a result he became the prey of morbid fear. Explaining how he spent his time, he said, "I get up early, read the obituary column, and if my name isn't there, I go back to bed."

—Kenneth Hildebrand

Special Article

The Role of Aviation Medicine Today and Tomorrow

JOHN C. DUFFY, M.D.
Rochester, Minnesota

At 35,000 FEET above sea level, the temperature is constant at minus 55° Centigrade, and the atmosphere is one-fourth that of the earth's normal composition. If you are one of the millions of air travelers this is the environment outside your window as you fly in one of today's modern jet aircraft. This hostile environment of the sky, and its effects on those who fly in it, is the particular study of a relatively new branch of medical science.

The brief evolution of aviation, which now stands on the threshold of space, has created complex problems, both for man and for his machine.

Aerospace Medicine

Aerospace medicine is a "branch of medicine concerned with the study, prevention, cure, or alleviation of diseases or other bodily ailments arising from conditions encountered in, or brought on by, flight through the atmosphere, or through space."[1] As is the case with all specialties, there is a required program of training for certification in aviation medicine. Instead of creating a new Board, aviation medicine was incorporated within the framework of the American Board of Preventive Medicine, which offers certification as a Diplomate in Aviation Medicine.

The major portion of training in aviation medicine is conducted by the military. At present, there is only one civilian residency in the field: a three-year residency at Ohio State University. The first two years are concerned with lectures, research, and field work; the third year is a preceptorship at some aviation institution. The typical military program is a five-year one, the added two years involving the practice of the specialty under the supervision of a board-certified specialist in aviation medicine.

Organization

The Aerospace Medical Association was founded in 1929. Today it numbers among its

Continued

affiliated societies the Airline Medical Directors Association, Civil Aviation Medical Association, Space Medicine Branch, and the Society of Air Force Flight Surgeons.

The Aerospace Medical Association and its journal, Aerospace Medicine, are in the forefront of scientific and technologic achievement in aerospace medicine. Its stated objectives are to advance the science and art of aerospace medicine; to establish and maintain co-operation between the medical group and other sciences concerned with aeronautical and astronautical development and progress; to promote, protect, and maintain safety in aviation and astronautics.

Categories of Concern

The major areas of concern for the specialist in aviation medicine may be conveniently broken down into the following categories: ailments resulting from different kinds of flight; evacuation of the sick and the wounded by air; selection, maintenance, and treatment of man as a flyer or space traveler; the adaptation of man to the conditions of flight; and the design of aircraft and related equipment to meet human requirements in flight.

Aeroembolism

The environment of flight and the demands it places upon the air traveler have resulted in some interesting medical ailments. For the pilot, the conditions of aeroembolism, barotrauma, and hypoxia are an ever-present concern. Aeroembolism, or the "bends," is a condition of altitude, which results in painful cramping in the joints, thought to be due to microair embolism. Changes in barometric pressure in ascent or descent in aircraft may adversely affect the sinuses and ears, resulting in uncompensated pressure differentials with subsequent barosinusitis and barotitis media. With dependence upon an artificial system to supply oxygen at high altitude, hypoxia, secondary to system failure, is an ever present hazard.

Hypoxia

Of practical concern to the passengers of our modern jet airliners is their cruising altitude of more than 35,000 feet. Any oxygen or pressure system failure at such altitudes places the passengers in an acute, hypoxic environment. All these planes are equipped with individual passenger oxygen systems; an oxygen mask is automatically presented to the passenger if the cabin altitude rises above the normal limit (usually over 12-15,000 feet).

Phlebitis

A recent clinical entity for passengers on long, intercontinental flights is "passenger phlebitis,"[2] associated with prolonged immobility in the sitting position. Often, there is a prior history of phlebitis in these passengers.

Physical Fitness

As greater numbers of people travel by air, the question of medical fitness to fly is asked of the physician with increasing frequency. In order to assist him in answering such questions, the Committee on Medical Criteria of the Aerospace Medical Association has published a comprehensive review of the medical criteria for passenger flying,[3] dealing with specific clinical entities and how they might be affected in flight. A familiarity with the contents of the article is mandatory for any physician who wishes to intelligently advise his patients with reference to their medical conditon and commercial flying.

Danger From Aspiration

The Second World War and the Korean conflict provided considerable experience in the evacuation of the sick and wounded by air. As a simple rule of thumb, any patient whose medical condition permits movement by any means may be safely evacuated by air. Fracture of the jaw or other conditions which require fixation of the jaw must be evaluated with care, as aspiration from air sickness is a serious problem.

The Crew

Perhaps the greatest responsibility of the military and civilian air surgeon is the selection and medical support of the pilot and aircrew members, as commercial and military pilots must meet very strict medical standards in order to maintain their flying status. Somewhat less stringent physical standards are set for private pilots. However, all categories of pilots and other responsible personnel must take frequent, periodic physical examinations. If the examination reveals a minor physical defect, the pilot may continue to fly with a waiver for the defect. Such a waiver is carefully evaluated each year by the physician and a decision made as to whether the waiver may be extended for another year.

Aircraft Accidents

One of the more grim tasks of the aviation physician is the investigation of aircraft accidents. He is a member of the team which the Federal Aeronautic Association sends to the scene of a plane crash. In a major airline accident he assists local medical personnel in the techniques used for the identification of crash victims; he also supervises the autopsy examination of the crew members involved in the crash and reviews the medical histories of the crew. His report to the accident investigation board will point to any physical condition or health factor which may have played a role in the accident.

Crop Dusting Pilots

An example of aviation-medicine detective work involved crop-dusting pilots, who had a high accident and fatality rate. The flying itself was dangerous and at low altitude, and the aircrafts were of ancient vintage with minimal engine maintenance. But these factors alone were not enough to explain their alarmingly high accident rate. During an autopsy on one of these pilots, the physician had a section of tissue removed and sent for special tests. His guess proved right: high concentrations of the chemicals used to dust the crops were found in the tissues. Thus it was clearly established that the pilots had inhaled the spray as they made their dusting runs. Immediate steps were then taken requiring the pilots to wear protective face masks.

Comments

The encouragement of flying safety and environmental health is of prime concern; health hazards, both physiological and physical, pose a real challenge. Toxic fuels, chemicals, and high frequency noise are but a few of the potentially dangerous environmental problems in aviation today.

Perhaps the best known phase of aviation medicine is related to our space efforts. One of the newest centers for the study of aerospace medicine is at Brooks Air Force Base, Texas, the USAF Aerospace Medical Center. It was there that the final phase of testing for selection of America's astronauts was carried out. The Center continues to conduct selection of future astronauts as well as research studies into the problems of space travel.

The ever-broadening scope of medicine in man's endeavors, will be well represented in man's conquest of space. The future of aviation medicine today is as limitless as the space in which it will practice tomorrow.

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1. Aerospace Glossary. Woodford Heflin, Editor. Air University September 1959.
2. Noreff, M. J.: 30th Annual Meeting of the Aerospace Medical Association, 1959.
3. The Committee on Medical Criteria of the Aerospace Medical Association. Aerospace Med 32:369, 1961.

Photographic Contest

The Doctor's Photographic contest continues each month. Send in your entries to the Photo Contest Editor, MINNESOTA MEDICINE, in accordance with the rules on page 34 of the January issue. The winning photograph each month will be printed on the cover of a subsequent issue of MINNESOTA MEDICINE.

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CSO-9193

History of Medicine

John Hunter

John Hunter (1728-1793) was the biologic Titan of his time. This uncouth and ungrammatical Scotchman was a physiologist, a philosopher, and a surgeon. He began his career at dissecting by assisting his distinguished brother, William Hunter. Soon he was teaching anatomy, and, like his brother, became an enthusiastic collector not only of anatomical preparations, but of books and manuscripts: a passion which was so great that in later years the museum of the Royal College of Surgeons was mainly grounded by his extensive collection. To his experience as an Army surgeon we owe many improvements in military surgery. "In his remarks on gunshot wounds, he laid down some fundamental principles often overlooked today and revealed the fact that he possessed that rare accomplishment, masterful inactivity. When he emphasized the importance of not enlarging wounds, but of frequently leaving them alone unless something necessary was to be done, he proved himself a master surgeon."

After leaving military duties at Belle Isle, Hunter returned to London and organized his school of anatomy. He was an ardent investigator. Because of his insatiable desire for knowledge he is now recognized as the founder of experimental and surgical pathology. In his search for specimens to dissect: "He spared neither expense nor trouble to himself or his friends to obtain the kind of animal he desired. He was undoubtedly 'one of the greatest collectors ever known, and scoured the world through friends and messengers for the flora and fauna of all lands.' As soon as he had accumulated ten guineas he would purchase some additions to his collection of animals. Not infrequently he borrowed from his friends. 'Pray, George,' he said to one of his good friends, a book seller, 'have you any money in your pocket? Have you five guineas? If you have and will lend it to me, you shall go halves.' 'Halves in what?' inquired his friend. 'Why halves in a magnificent tiger which is now dying in Castle Street.' His friend lent the money and John got the tiger."[2]

He continued his studies and collection at his country house at Earl's Court, then outside of London. Never before had so many kinds of birds and animals been assembled on the grounds of a country mansion. The maintenance of this menage required fifty servants. "Hunter was perpetually on the lookout for rare beasts. If a gipsy passed by with a dancing bear, Hunter would make a bargain with the man to bring the creature for dissection when it died.

The Irish giant cost Hunter much labour and a great deal of money. He was . . . determined to have O'Bryan's skeleton. . . . When the giant fell sick, Hunter had him kept under observation. But the Irishman scented danger, . . . regarding with horror the thought that his body would be cut up, he made his friends promise that when he died they would never lose sight of his corpse until it had been sealed up in a leaden coffin and

Continued

sunk in the sea. We are told that bribery and corruption to the tune of 500 sterlings were needed before Hunter got his way. The upshot was that the skeleton is in the Royal College of Surgeons' museum, and that O'Bryan's name has become immortal."[3]

By 1767, John Hunter was rapidly winning recognition on his own, no longer basking in the fame of his celebrated brother. That same year he was elected a fellow of the Royal Society, which honor was not conferred on brother William until three months later. John was elected a Surgeon to St. George's Hospital in 1768, an appointment which gave him income for his extensive experiments, as well as providing opportunity to attend the living, examine the dead, and share the pupils' fees, with the privilege of taking apprentices.

In 1771, Hunter married Miss Anne Home, the daughter of a military surgeon. Typical of his blunt personality, is a letter which he wrote to his brother on the eve of his wedding:

"Dear Brother, — Tomorrow morning at eight o'clock and at St. James's Church, I enter into the Holy State of Matrimony. As that is a ceremony which you are not particularly fond of, I will not make a point of having your company there. I propose going out of Town for a few days; when I come to Town I shall call upon you. Married or not married, ever yours,

John Hunter."[4]

However, in spite of his grim announcement, the marriage proved to be a very happy one. Mrs. Hunter added a cultural atmosphere to their home, and under her influence the rough edges of John's uncouth nature were smoothed off.

By 1775 he was delivering his course of Lectures on the Principles and Practice of Surgery, consisting of nearly one hundred lectures. It began in October and continued until April, being given every other evening from 7 to 8 o'clock. The fee was four guineas. At some Courses there were as many as fifty in attendance; however, due to unfavorable publicity after his publication of his TREATISE ON THE VENEREAL DISEASE, the group dwindled to twelve. "There is a story that at one Course there was only one pupil present, and that in order to be able to begin his address with the word 'Gentlemen,' Hunter ordered the attendant to bring in the skeleton."[5]

In 1787 he received the Copley Medal of the Royal Society and was elected a member of the American Philosophical Society. Sir Joshua Reynolds painted his portrait which is now at the Royal College of Surgeons. "The story of the painting has often been told. John Hunter was a bad subject, and the almost finished portrait was not a success: when one day, during a sitting, he fell into deep thought. Reyonlds instantly turned the canvas upside down and painted a new head between the unfinished legs."[6]

The last years of Hunter's life were ones of unceasing toil. He held himself to a rigorous schedule of rising before six in the morning and working until two the next morning. He pursued this pace until his death in 1793.

John Hunter's contributions to medical progress are legion, but his " . . . main significance was that he threw open the field of surgical observation and experiment to general medicine, enabling all doctors to turn it to account . . . he constructed the first bridge between surgery and medicine."[7]

So memorable were the achievements of this great Scotchman, that at the Royal College of Surgeons there is given annually a "Hunterian Oration" intended to commemorate his labors or to portray some lesson from his life and work.

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Psychosomatics: "Mind Over Matter" — Galen

An astute observer, Galen discovered that when physical causes failed to account for physical symptoms, persistent patience and a little adroit inquiry eventually disclosed an emotional cause for hitherto inexplicable disorders.

One of Galen's lady patients happened to be secretly infatuated with a male dancer, a passion inducing an elusive malady: restlessness, insomnia, temperamental behavior — accentuated by irregular pulse and change of color on hearing the name of the man she loved.

Another patient, a slave, was suffering conspicuous weight loss and severe insomnia, due to anxiety that he might be called upon to account to his master for sums of money that might prove deficient.

Euphemism

That which we call sin in others is experiment for us.—Emerson

---

Where others lie, we are clever; where others cheat, we are shrewd and canny; where others are badtempered, we are righteously indignant; judging others, we would call their conduct selfish; judging ourselves, we call it practical.

—Henry Emerson Fosdick

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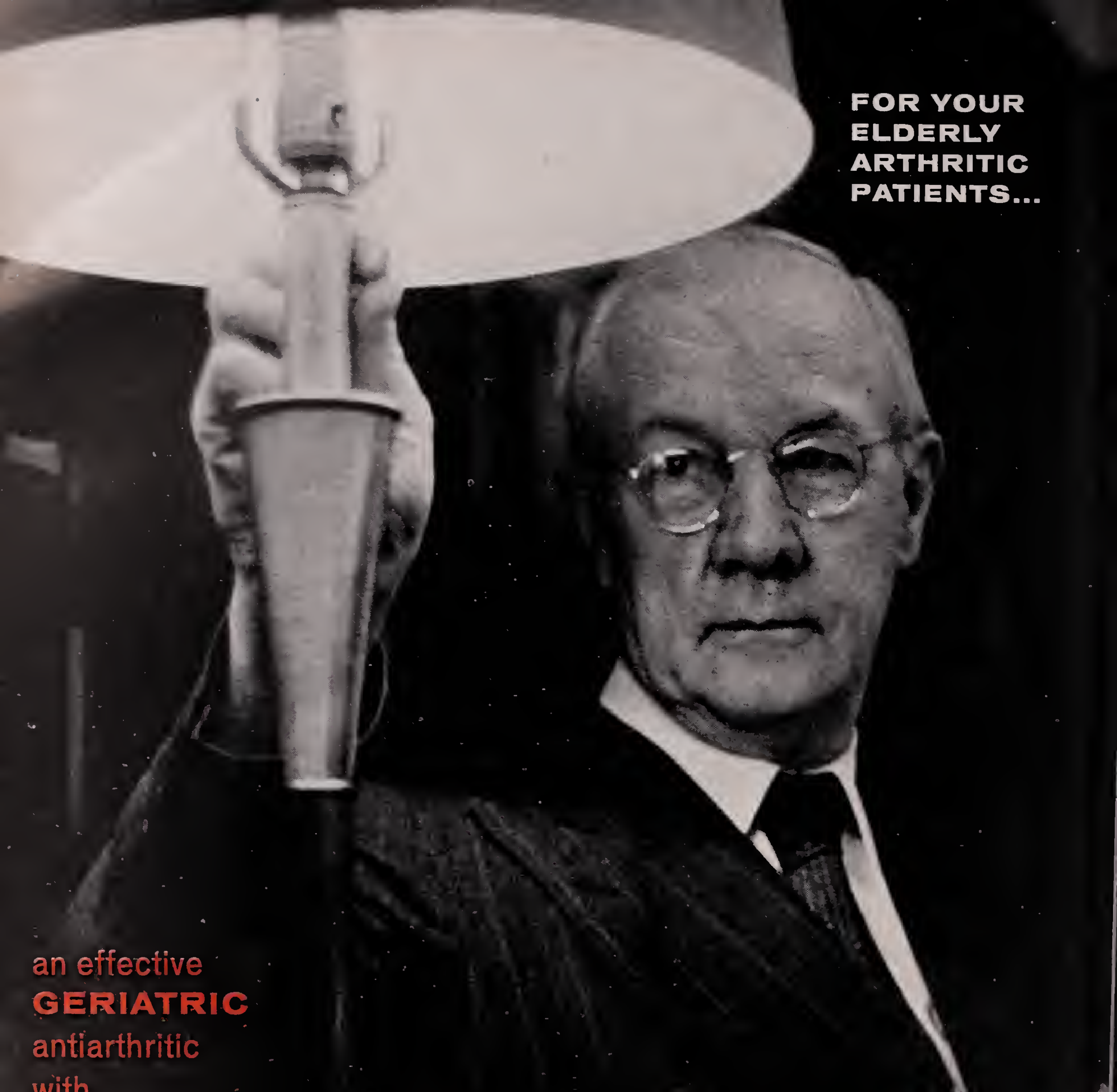

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Meetings and Announcements

The joys of meeting pay the pangs of absence; else who could bear it?—Rowe

JULY

American Diabetes Association, Royal York Hotel, Toronto, July 24 Info: J. Richard Connelly. 1 E. 45th St., New York 17.

American Dietetic Association (members only), Portland Hilton Hotel, Portland, Ore., July 28-31. Exec. Sec.: Ruth M. Yakel, American Dietetic Association, 620 N. Michigan, Chicago 60611.

American Veterinary Medical Association, Conrad Hilton Hotel, Chicago, July 19-23. Exec. Sec.: H. E. Kingman, Jr., DVM, 66 S. Michigan, Chicago 60605.

New Mexico Academy of General Practice, Ruidoso, July 20-23. Sec-Treas.: Herschel L. Douglas, M.D., Box 767, Tatum.

Rocky Mountain Cancer Conference, Brown Palace Hotel, Denver, July 10-11. Chmn.: N. Paul Isbell, M.D., 1809 E. 18th Ave., Denver 80218.

AUGUST

American Academy of Physical Medicine and Rehabilitation, Statler-Hilton Hotel, Boston, Aug. 24. Pres.: Morton Hoberman, M.D., 5900 Arlington Ave., Riverdale 71, N. Y.

American Association of Blood Banks, Shoreham Hotel, Washington, D. C., Aug. 25-28. Info.: Lois J. James, 30 N. Michigan, Chicago 2.

American College of Surgeons (Montana chapter), East Glacier, Mont., Aug. 22. Sec-Treas.: W. H. Randall, M.D., Miles City Clinic, Miles City, Mont.

American Congress of Physical Medicine and Rehabilitation, Statler-Hilton Hotel, Boston, Aug. 23-28. Exec. Dir.: Glenn Gullickson, Jr., M.D., 30 N. Michigan, Chicago.

American Hospital Association, Palmer House, Chicago, Aug. 24-27. Dir.: Edwin L. Crosby, M.D., 840 N. Lake Shore Dr., Chicago 11.

American Institute of Ultrasonics in Medicine, Statler-Hilton Hotel, Boston, Aug. 22. Sec-Treas.: Edwin Matlin, M.D., 220 Stewart Ave., Garden City, N. Y.

American Society of Pharmacology and Experimental Therapeutics, Inc., University of Kansas, Lawrence, Kan., Aug. 23-27. Sec.: Sidney Udenfriend, 9650 Wisconsin Ave., Washington 14, D. C.

American Society of Human Genetics, Boulder, Colo., Aug. 22-28. Sec.: Samuel H. Boyer, M.D., Johns Hopkins Hospital, Baltimore 5.

International Conference on Preventive Cardiology, University of Vermont, Burlington, Vt., Aug. 24-28. Info.: W. Raab, M.D., 206 Summit St., Burlington, Vt., 05401.

National Medical Association, Statler Hotel, Washington, D. C., Aug. 2-6. Exec. Sec.: John T. Givens, M.D., 1108 Church St., Norfolk 10, Va.

Rocky Mountain Radiological Society, Brown Palace Hotel, Denver, Aug. 20-22. Sec-Treas.: John H. Freed, M.D., 4200 E. Ninth Ave., Denver 20.

West Virginia State Medical Association, Greenbrier Hotel, White Sulphur Springs, Aug. 20-22. Exec. Sec: William H. Lively, Box 1031, Charleston, W. Va. 25324.

Wyoming State Medical Society, Jackson Lake Lodge, Moran, Aug. 31-Sept. 3. Exec. Sec.: Arthur R. Abbey, Box 2266, 4020 House Ave., Cheyenne.

SEPTEMBER

American Association of Medical Clinics, Americana Hotel, Bal Harbour, Fla., Sept. 16-18. Sec.: R. S. Condie, M.D., Palo Alto Medical Clinic, 300 Homer Ave., Palo Alto, Calif.

American Association of Obstetricians and Gynecologists (members and invited guests), Homestead, Hot Springs, Va., Sept 10-12. Sec.: Clayton T. Beecham, M.D., 3911 Vaux St., Philadelphia 29.

American College of Obstetricians and Gynecologists (District 2), Concord Hotel, Lake Kiamesha, N. Y., Sept. 24-27. Exec. Dir.: Donald F. Richardson, 79 W. Monroe, Chicago 3.

American College of Obstetricians and Gynecologists (District 7), Dinkler-Tutwiler Hotel, Birmingham, Ala., Sept. 25-26. Exec. Dir.: Donald Richardson, 79 W. Monroe, Chicago 3.

Methodist Hospital Annual Symposium Sept. 19 in Minneapolis. Subject of symposium "Current Management of Diabetes Mellitus."

ANNOUNCEMENTS

University of Colorado Medical Center postgraduate calendar:
July 20-25—General Practice Review
Write: Postgraduate Medical Education, 4200 East Ninth Avenue, Denver, Colorado.

Rochester . . .

The key to the city of Rochester was presented to American Medical Association President, Doctor Edward R. Annis, at the closing session of the House of Delegates by Lawrence Potter, President of the Rochester Chamber of Commerce. Doctor Annis was an honored annual meeting guest.

Joining the ranks of Fifty Club members was Doctor Norman M. Keith, Rochester. Recognition and citations were presented to 14 new fifty club members at the Annual Banquet.

Post banquet entertainment was provided by the Zumbro Medical Society and Auxiliary. Activities included a floor dancing, and a late evening buffet.

Medical Economics

Annual Meeting Included Mayo Centennial Tribute

In Rochester. . .

A centennial tribute to the Mayo Clinic, an outstanding scientific program and important actions by the House of Delegates were some of the highlights of the 111th Annual Meeting of the Minnesota State Medical Association, May 18, 19, and 20 in Rochester.

American Medical Association President, Doctor Edward R. Annis, told delegates Tuesday morning at their closing session, that the Kerr-Mills Act is in good shape but still needs "upgrading" in areas where it is not doing an adequate job. "The better the job we do with Kerr-Mills the better are our chances with the people and through them their legislators," said Doctor Annis.

"We must be vigorous in our campaign to inform and educate the public as to why it is to their advantage to remain free in the medical profession" emphasized Doctor Annis.

Doctor Annis, commenting on the physician strike in Saskatchewan and more recently in Belgium, said the doctors did not actually strike but were "locked out" by governments who wanted to do away with private practice of medicine in favor of government controlled medicine.

Delegates approved a reference committee recommendation calling for the formation of physician utilization committees to prevent the abuse of hospital utilization. The committees would be formed by hospital staffs. The reference committee in its presentation to the House, pointed out: 1) This is not a mandatory program; 2) It does not affect hospital accreditation; 3) That the utilization committee is made up of physician members only appointed by the hospital staffs; 4) Utilization committees are not punitive and do not reflect on any particular medical group.

The delegates also:

Approved a study of the Blue Shield sales, fees and administrative policies.

Authorized the appointment of a committee on fees to handle all questions relating to fees for medical services to Kerr-Mills recipients.

Voted confidence in Doctor Robert N. Barr, State Health Officer, currently under attack by some Minnesota legislators for his strong position on water pollution.

Labelled cigarette smoking as a health hazard.

Opposed amendments to the Kintner Regulations issued by the Internal Revenue Service. They would not recognize the right of physicians organized under the Minnesota Professional Corporations Act and similar acts in other states to be taxed as corporations under federal law.

Expressed appreciation to the Minnesota Chapter of the American Association of

Continued

Note: Photos courtesy of Rochester Port Bulletin.

Congratulations were extended to Doctor J. Minott Stickney, Rochester, President-elect, by Doctor J. P. Medelman, St. Paul. Elections were held at the concluding session of the House of Delegates at Rochester.

Technical exhibits at the Mayo Civic Auditorium topped the mark. More than 1200 physicians visited the technical exhib during the three-day meeting.

A new product . . . Latest drugs and other medical supplies were shown to doctors who stopped to visit with technical exhibitors.

NASAL INJURIES
MANDIBULAR FRACTURES
MAXILLARY FRACTURES
ZYGOMAT

Scientific exhibits representing new medical techniques drew attention of physicians attending the scientific sessions at Annual Meeting.

Medical Assistants and its national organization for the dedicated and unselfish assistance and work in the combined goals of both organizations.

Delegates who favor the Taconite amendment were urged by the Resolutions Committee to cast a *YES* ballot in the November election. Failure to vote is in effect a *NO* vote on the amendment.

Commended the World Medical Association and its President, Doctor Edward R. Annis, for its work in fostering the dissemination of medical science through the free practice of medicine.

A check for $14,586 was presented to the University of Minnesota Medical School at the Sunday afternoon session. A grant from the American Medical Association Education and Research Foundation (AMA-ERF), the check represents gifts from Minnesota physicians to the University of Minnesota. The money is part of more than a million dollars contributed to medical schools by physicians and their families throughout the country last year.

Doctor J. M. Stickney, Rochester, was named President-Elect at the closing session of the House of Delegates. Presently Doctor Stickney is serving as a delegate to the American Medical Association and he was also reelected to that post. Other officers elected included Doctors J. Richards Aurelius, St. Paul, First Vice-President; G. R. Diessner, Rochester, Second Vice-President; Barnard Hall, St. Paul, Secretary; Karl W. Anderson, Minneapolis, Treasurer; John L. Falls, Red Wing, Speaker of the House of Delegates; John T. Pewters, Minneapolis, Vice Speaker of the House of Delegates; H. E. Wilmot, Litchfield, Councilor of the Third District; D. R. Gillespie, St. Paul, Councilor of the Fifth District; W. J. Deweese, Bemidji, Councilor of the Seventh District; A. O. Swenson, Duluth and Doctor Stickney, Rochester, Delegates to the American Medical Association; and C. L. Oppegaard, Crookston, and Donald McCarthy, Minneapolis, Alternate Delegates to the American Medical Association.

Doctor Robert N. Barr, Secretary and Executive Officer of the Minnesota Department of Health was named recipient of the Minnesota State Medical Association Distinguished Service Award. Doctor Barr, who received his first appointment with the Minnesota Department of Health in 1934 was appointed to the post of Secretary and Executive Officer in 1955. He succeeded Doctor A. J. Chesley as State Health Officer. At the presentation ceremony Doctor Buckley commended Doctor Barr for his devoted service in a wide variety of public health programs, especially those dealing with tuberculosis, poliomyelitis, hospitals, nursing homes, care of the aged, all phases of rehabilitation, safety, radiological health, water pollution and the health and welfare of the nation.

Also honored at the Banquet held in conjunction with the meeting were fourteen Minnesota physicians who have practiced medicine for 50 years. Physicians receiving 50 year citations and awards included: Doctors George I. Badeaux, Brainerd; Robert L. Bowen, Hibbing; Edward M. Bratrud, Alexandria; Lowell M. Campbell, Minneapolis; James W. Crump, St. Paul; Elmer O. Dahl, Minneapolis; Richard N. Jones, St. Cloud; Norman M. Keith, Rochester; Katherine A. Nye, St. Paul; M. A. Shillington, Fort Lauderdale, Florida; Olof I. Sohlberg, St. Paul; Carl A. Traeger, Faribault; Frederick A. Willius, Rochester; and Herbert M. Wynne, Minneapolis. Fifty club awards were presented by Doctor John L. Falls, Red Wing.

Doctor Lloyd G. Stevenson, New Haven, Connecticut, Professor of Science and Medicine, Yale University, banquet speaker presented a centennial tribute to the Mayo Clinic and Foundation, and a tribute, also, to the University of Minnesota Medical School currently observing its 75th year.

Presiding at the banquet was Doctor John Paul Medelman, St. Paul, President of the Minnesota State Medical Association.

Official registration figures indicated that a total of 2,444 persons including 1,216 doctors attended the meeting.

Minneapolis was selected as host city for the Annual Meeting in 1965 because the American Bowling Congress will be meeting in St. Paul at that time. The dates for next years meeting are May 17, 18 and 19.

In Appreciation

The Minnesota State Medical Association would like to express its appreciation to the firms listed below. These firms were technical exhibitors during the recent 111th Annual Meeting of your Association. Their participation in our annual meeting contributed much to its success.

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The Blue Shield

Comments to the Minnesota Medical Service, Inc., Corporate Body Meeting

May 16, 1964

Ira C. Layton, M.D.

We as physicians must have two goals in our professional lives — the provision of the finest medical care possible for those who seek our services, and the preservation of the system of free practice which has made American medicine the unquestioned leader and the envy of the world.

These goals can be achieved only by strengthening and expanding existing methods for the voluntary prepayment of health care. Strengthening and expansion of this total movement must come as a result of leadership by Blue Shield and Blue Cross, physician and hospital sponsored respectively.

We are well aware that the advancements of medical science are not available free of charge. The best medical care is not to be had by those of even average means except at expense frequently beyond their ability to pay at the time of illness. Three methods of payment are potentially available — first, postpayment . . . the time-honored but presently impractical approach to medical care costs attended with debt, anxiety and, often, unbearable strain on incomes already overtaxed by life's necessities and installment credit. Horse-and-buggy medical practice is long gone and with it, of necessity, is going horse-and-buggy postpayment for health care fees. Second, prepayment of anticipated costs, using funds voluntarily deposited with prepayment plans available in adequate amounts as a result of pooling and adherence to insurance principles. The third possible solution, obviously, is the utilization of funds provided at great tax and national debt burden by the federal government with the usual strings attached. Your patients are now well informed and keenly aware of the miracles of modern medicine. They will not be denied at their time of need. It is up to you who shall be the purveyor. I am sure you agree with me that preservation of the free practice of medicine is in the public interest and can only be accomplished by strengthening voluntary prepayment plans.

In order to evaluate our current position and to assess our future needs, it would perhaps be well to review the past briefly. A vast majority of Blue Shield plans have in recent years celebrated their twentieth anniversary, and a few their twenty-fifth. Impetus was given to their development by proposed social legislation bearing the names Wagner, Murray, and Dingell. Although such proposed social legislation stimulated development of Blue Shield, it was inevitable that methods of prepayment would be devised for then, as now, even those families of average income found it difficult to meet more than the most routine of medical expenses. Refusal on the part of commercial insurance companies to enter such new and untried fields

Continued

as medical care insurance led to the development by members of the profession of individual Blue Shield plans, enabling patients to prepay significant portions of their medical care expenses. These plans developed in response to public need and through no desire on the part of medicine to enter into the insurance business. Then, as now, most such programs developed with the intent of making full payment to the physician for covered services rendered to individuals of average or below-average income. Too often, one hears the comment that Blue Shield originated for the indigent. Those who speak in this manner have forgotten the extent of inflation for, at that time, the commonly used $3,000 service income level provided potential service benefits for as much or more of the population than does the present frequently used $7,500 income level.

Although the various Blue Shield plans had individual local origin and, consequently, minor differences, certain basic concepts are common to them all which set them apart from commercial insurance. Most obviously, they originated as non-profit organizations. Absence of profit motive and the business of helping the doctor's patient pay for necessary medical care eliminated "third-party" interference in the patient-doctor relationship. Ultimately, the non-profit nature of these organizations has meant that approximately 90¢ out of every premium dollar is returned to the subscriber in benefits. Blue Shield plans, generally, were community oriented. There has never been intent on the part of Blue Shield to select only the best health prospects for coverage. To do so would defeat the purpose of providing benefits to those who need it most. Soon after the origin of these plans and as actuarial experience was gained, prepayment through Blue Shield was gradually made available to all . . . at premium rates which spread the cost of protection over the entire community. Even in areas where experience rating is used, a community factor is often employed to maintain a community rate concept. From their inception, Blue Shield plans have provided continuous enrollment to their subscribers and, for all practical purposes, have provided non-cancellable coverage. Finally, and most important, Blue Shield plans originated and have remained under the control of sponsoring physicians, usually state or county medical societies. The spontaneous growth and overwhelming public acceptance of these programs is a matter of record. From humble beginnings twenty-odd years ago, Blue Shield plans now cover approximately fifty million people. In this brief time, Blue Shield has done for us in the economic field a job somewhat equivalent to what it took many generations to achieve in the scientific sense in medicine.

As a result of such rapid growth, contact has been lost with sponsoring physicians, leaving both these physicians and Blue Shield each uninformed regarding the other's problems. In this atmosphere, it was inevitable that some loss of support for the local plans would occur. Without support of individual physicians, Blue Shield has no meaning and cannot survive. Without Blue Shield, the practice of medicine as we know it today, similarly, will die. Blue Shield and the medical profession have in some areas grown so far apart that individual physicians have been heard to express little concern as to whether they dealt with Blue Shield or the federal government. Inadequate communication has produced such attitudes and loss of confidence. Support from organized medicine and individual doctors is the first hallmark of Blue Shield. For many reasons, this support is in grave cachectic condition. It is incumbent on governing boards to diagnose the wasting disease present and apply whatever drastic surgery must be performed to restore nutrition and vital functions.

Our immediate needs are to arouse the professional interest which led to the creation of these programs and assure a rebirth of confidence by demonstrating to doctors that it is not the expansion of Blue Shield which is our goal but, rather, the preservation of free medical practice. It is imperative that the plans re-evaluate their professional relations programs. I refer not to the weekly mailings of informational bulletins or to occasional visits by members of the professional relations staff. I refer, rather, to those plan policies which give assurance to the participating physician that Blue Shield is truly under control of the medical profession. Does that physician actually have a voice in the selection of those who represent him on the Board of Directors? If not, it is time for change. Are his opinions actually sought in the development of new fee schedules as service income limits are raised, in order to continue coverage for a majority of the population? If not, again, a change is in order. Does he have a group, other than the Board of Directors, to whom he may take a presumed injustice and be asured that his complaint will be received and seriously considered? If not, changes must occur. Will his suggestions for expansion of the scope of benefits be heard by an attentive audience who will take the time to explain the merits or impracticality of his suggestion? If not, it is time for change. Only when such assurances have been provided can the confidence of the participating physician be restored and maintained.

Another unique aspect of most Blue Shield plans, as compared with the commercial insurance companies, is the principle of full payment or so-called "service benefits." The guarantee of payment in full for covered benefits is the only true assurance of medical profession support which Blue Shield can give its subscribers. We have for several years, with increasing frequency, heard the profession criticized by members of the public. The declining esteem in which the profession is held has been repeatedly and well documented. For the most part, critcisms have had to do with the magnitude of fees charged and a lack of understanding of the services rendered. Much can be done to alter these impressions through the provision of increased income levels and adequate fee schedules. Here, again, full cooperation of participating physicians and sponsoring societies is mandatory. A service benefit program which provides full payment for only 10% of the population inevitably does more harm than good. A high grade indemnity program is preferable. If appropriate fee schedules are provided, with cooperation and advice from participating physicians, and service income levels are realistic, both physician and patient will have reason to be satisfied.

The local autonomy of Blue Shield plans has provided many benefits. More physicians have been associated with the direction of plan policies as a result. A greater flexibility has been available, making it possible to meet specific local problems. A broader variety of experimentation has resulted, with sharing of the results of this experimentation between plans, but local autonomy has drawbacks, too. Two-thirds of this nation's labor force is employed by companies operating across state lines. The frequency of individual transactions in business has been reduced. Union-management bargaining and the mergers of large corporations have led, quite understandably, to demands that uniform benefits be provided across the nation for employees of large companies. Although we have been able to provide fairly uniform benefits for the Federal Employees, by and large, the servicing of national accounts has been impossible. National accounts must be sold not only because of their size but because of their comparative good health. When competing for these groups, we constantly lose to commercial carriers for lack of a uniform national contract from Blue Shield. Continuation of this trend can result only in a reduction of good risk groups held by Blue Shield and, thereby, an increase in the proportionate number of high utilization subscribers. Increasing costs and potentially pricing Blue Shield out of the market for those who need it most — here, again, an open invitation to governmental intervention becomes apparent. The National Association of Blue Shield Plans has been well aware of this for years and has, during that time, made valiant efforts to achieve a uniform scope of benefits. Short-sighted local resistance has, for the most part, prevented accomplishment of this goal. The time is long past when we may consider ourselves isolated one from the other. Actions which you take in Minnesota may reflect quickly and directly upon subscribers and physicians in Kansas City. It is imperative for national contracts that we yield a bit

Continued

of our autonomy. In doing so, we must recognize that we are working for the public and the medical profession as a whole throughout the country as vigorously as we work for them at home. Benefits to be derived from national cooperation are considerable. By virtue of profits derived from low utilization groups, we can supply adequate coverage to the aged, the low income and others at a price they can afford to pay. Cooperation between local plans and the National Association is essential if we are to grow, as we must. There are other benefits to be derived from such close liaison. A very current example of these benefits is the "Test of Performance Survey" to begin on a national scale the day after tomorrow. With the cooperation of local plans and the medical profession, this survey will measure the performance of Blue Shield plans throughout the United States in terms of the relationship between plan payments for selected services and the amounts physicians bill patients for those same services. The feasibility of such a test has been appraised by pre-test studies in Massachusetts and Alabama. These surveys indicate conclusively that excellent response can be obtained from physicians when they are adequately oriented and, instead of criticism from physicians, enthusiasm was the rule. It is anticipated that this study will provide both national and local organizations with data of great value. This is but one of many ways in which the national organization stands ready to help local plans, from protection of the trademark to assistance in technical fields of plan operation.

This, then, is our present position — seventy-odd Blue Shield plans, providing prepaid medical care protection of varying qualities to fifty million subscribers and loosely joined together in a national organization, we are recognized by the public as a major item in our country's social progress. In cooperation with medical societies, hospitals, and Blue Cross, Blue Shield is capable of providing voluntary prepaid medical care of such quality and scope that government intervention would be rendered totally unnecessary. In some respects, our emotional maturity has not kept pace with our physical growth and petty problems impede our progress.

The evaluation of future needs is imperative. Bold actions, such as originated Blue Shield, are again essential. Earlier, the parties to medical care — doctors, hospitals, prepayment plans, insurers, and others could act independently. The magnitude of modern medicine makes such independent action now inadequate. The burden of supplying health care needs is shifting to the voluntary system as a whole.

Present protection must be strengthened. Surgical coverage trails hospital coverage by millions of subscribers. Medical coverage is even further behind. X-ray and laboratory benefits are only slightly more often included than omitted. We are faced with the need to supply some form of more inclusive coverage providing protection beyond the period of hospitalized illness. The initiative in this field has been seized by insurance companies with the marketing of "major medical." We must recognize that consumers are assuming a larger role in health care than they themselves realize. In originating contributions, determining benefits, and deciding eligibility, labor and management in the United States have taken over functions which in other parts of the world are assumed by government. The people are now in a continuous financial relationship through payment of dues with purveyors of health service. It is, therefore, small wonder that they and their representatives seek explanation for increased costs and increased utilization. No longer is an attitude of "Let us practice medicine and you pay the bill" acceptable. It is up to the physicians and hospitals to recognize the consumers do have a vested interest in the way medicine is practiced. A very real danger lies in increased utilization. Whether we like it or not, the control of improper use of expensive facilities must be exercised by physicians, hospitals and prepayment plans. Failure to do so may prove catastrophic. Subscribers have a right to the assurance that unnecessary elements of cost are not being passed along to them.

I have no panacea for the ills that beset us. Solutions to our problems must be devised by the cooperative efforts of all concerned — provider, purchaser and insurer. I do know, however, that means must be found to provide protection for low-income, high-use groups such as the aged, and to assure proper utilization of the facilities which modern science has made available.

If we are to achieve our originally stated goals of preserving the system of medical practice that has created the world's finest medical care, and of providing this medical care to people on a voluntary prepayment basis in order that they might avoid the economic catastrophe of serious illness, we must stand ready when necessary to relinquish a portion of local autonomy in order that the public and the profession may be better served throughout the nation. We must, through every means, restore the confidence which the profession felt for Blue Shield at its origin. Only then can we say with pride "This is the doctor's plan."

President's Letter Continued from Page 775

what the rapid emergence of Blue Shield as a competitor in the commercial insurance field means to us as doctors. We need to decide, on the basis of actual information, if this is truly "a doctors' plan." The committee, still to be appointed, will explore these matters in depth and report to the Council and the House of Delegates, possibly in a special session of the House, if findings warrant. A third action reflects a heightened awareness of a problem which has too often been swept under our organization rugs. This is the problem of disciplining our own members who violate our ethical code, and of seeing that justice is done. It is inherent in our position as responsible professional men that we should be more alert to infractions of our code than any law enforcement body could possibly be. By the same token, we should have the machinery for dealing promptly and impersonally with these infractions instead of covering them up, as we sometimes do, or leaving them to the police. It is not enough to tell ourselves, with truth, that the offenders are few in comparison, because the public image of medicine suffers every time one complaint is dismissed without a thorough and impartial investigation. Justice, the freedom of medical practice, and political wisdom all require that we handle these matters well. It is fortunate that the Council and the delegates authorized the essential first step toward a possible revision of our system for handling complaints.

One other action made me proud of the wisdom and good sense of our policy makers. In spite of some opposition, grounded more in misunderstanding than in genuine differences in philosophy, the House unanimously approved the utilization committee principle for curbing over-utilization and the consequent rising costs of hospital beds. Hospital staffs were encouraged to form their own utilization committees at their own discretion, in case of need. They were to be informed that utilization committees have nothing to do with insurance companies, or with licensure, or accreditation. They are simply a way for the doctors, themselves, to take the lead in curbing over-utilization. By so doing they may well anticipate and avoid the interference of state officials in what should be exclusively the doctor's responsibility. That the method works is shown by the highly satisfactory experiment at St. Mary's Hospital in Duluth, and in other hospitals and states all over the country.

Official proceedings will be in the hands of delegates and county societies within a few weeks. It is my hope that they will be studied carefully by everybody who is interested in what medicine is really doing in Minnesota to maintain its leadership in social and economic matters which concern medicine, as well as in scientific development for the care of the sick.

J. P. Medelman M.D.

J. P. Medelman, M.D.
President
Minnesota State Medical Association

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Coulomb. Dr. Max Nordau left a most vivid description of the hospital conditions at that time, stating that it would often be found that in a moderate-sized bed there would be four, five, or six sick persons beside each other, the feet of one to the head of another; children beside grayhaired old men; indeed, incredible but true, men and women intermingled together; persons with infectious diseases beside others who were only slightly ill and often body against body; a woman groaning in the pangs of labor lying next to a patient suffering from typhus and delirious with fever.

The gray-haired fathers of Paris recognized the need of having L'Hotel Dieu located in the center of Paris and the people rallied in support of their institution of healing, teaching, learning, and searching into human illness. Thus L'Hotel Dieu persists in its ancient venerated walls. Tenon and his treatise had a maturing influence on the subsequent improvements carried out in the Paris General Hospital and throughout the civilized world.

Karel B. Absolon, M.D.*
Minneapolis, Minn.

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*From the Department of Surgery, University of Minnesota, Minneapolis, Minnesota. Supported by USPHS Grant #0697-5260.

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Acknowledgments

Mrs. J. Smith, University of Minnesota Biomed. Library. Illustrations from the Archives of History of Surgery, University of Minnesota, School of Medical Sciences, Minneapolis, Minnesota.

Medical History

Medical history is world history. Some phase of medicine has been involved in every great historical event, but usually these medical aspects have been ignored or overlooked. Consequently, when you turn to them they take you away from the beaten path of history and lead you instead into little-known byways of history. Yet, for everyone, medical history is probably more important than any other phase of history, for medical history discloses the forces that have made our modern civilization possible.

Howard W. Haggard, M.D.: "The Lame, the Halt, and the Blind"

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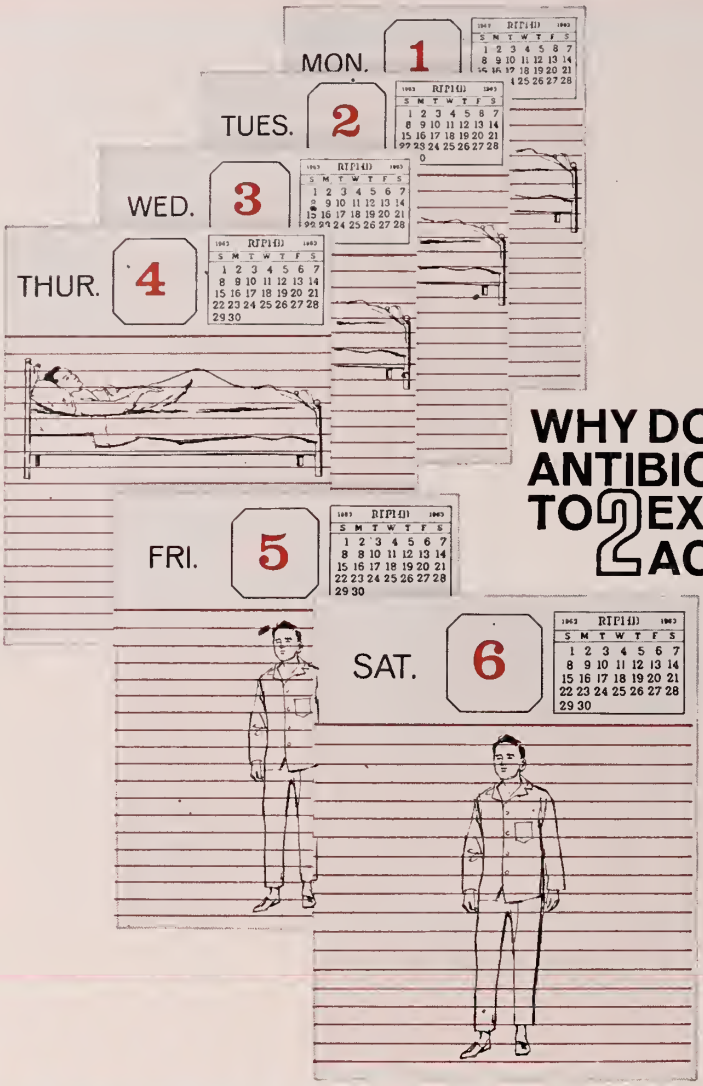

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President's Letter

The American Medical Association has recently issued an interesting report on Physician-Hospital relations. The council on Medical Service became concerned by developments in the area of providing medical care in hospitals. These developments included the appointment in many hospitals of salaried physicians in many capacities covering posts from chiefs of staff down through physicians who furnish care ordinarily provided by interns and residents. In 1961, the Council instructed its Committee on Medical Facilities to study these and other changes in relation to their impact on relationships of physicians and hospitals. The report is lengthy (186 pages). One section of it deals with the expansion of hospital functions, a matter to which all physicians should give thought.

The role of the hospital in community health care has been fostered by advances in medicine and methods of financing advanced care. Specialization has increased at an amazing rate. This has resulted in more closely drawn lines of staff organization in hospitals. There were increases in services offered by hospitals in the years between 1952 and 1962, ranging from 21% in diagnostic X ray to 43% in physical therapy, 98% in electroencephalography, and 362% in radioactive isotopes. And these figures do not completely reflect the unit care picture as the hospitals trend toward outpatient coverage, as opposed to primarily inpatient service.

Hospitals have become deeply interested in rehabilitation. The American Hospital Association has a committee which functions to develop plans for promoting restorative medicine programs.

Hospital services are also being offered to outpatients in their homes. In 1962, 205 short-term general and special hospitals had home care programs.

Hospitals recognize the need for assuring long-term care by providing units for such care. In 1962, a study showed that 488 hospitals maintained a nursing home unit for patients requiring nursing care but not the full range of hospital services.

There has been a tremendous growth in the use of emergency and outpatient departments in hospitals. In the year 1958, compared to 1945, a group of 300 hospitals across the nation showed a 120% increase in total outpatient visits. There are several factors responsible for this situation. Prepayment insurance plans play an important part. Blue Cross payments per 1000 members for inpatient care increased from 100 to 142 between 1947 and 1961, while outpatient care payments rose from 12 to 61 per 1000 members. Many services formerly done in the physician's office are now performed in hospitals. Physicians and county medical societies are aware of the need for emergency medical care. In 1963, there were 517 county societies with 123,000 members sponsoring emergency call plans.

Continued on Page 1016

thrown for a loss...

Keeping flies out of pharmaceutical production areas is important, yet entrances must accommodate heavy traffic of people and materials. In fact, at Eli Lilly and Company, the entrances to certain production facilities where traffic is heaviest have no screens or doors. ☐ This makes it look easy for flies to get in. But let one try it and he is literally picked up by a fast-moving blast of air and thrown for a loss—back outside. This "curtain of air," moving down and out from the top of the open doorway, bars the entrance and keeps flies out . . . still another step demonstrating the care that goes into the finished product.

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Elective Induction of Labor

F. L. SCHADE, M.D.*
E. P. SEISLER, M.D.*
Worthington, Minnesota

MANY OBSTETRICIANS adhere to the traditional, conservative viewpoint that good obstetrical care demands that patients be allowed to go into spontaneous labor unless interruption is indicated by some obstetrical or medical complication. Others are more liberal and advocate elective induction of labor, supporting their position for the following reasons:[1]

1. To prevent uncontrolled delivery prior to or immediately upon arrival at the hospital.
2. For the peace of mind of the patient who fears she might have an uncontrolled delivery because of distance from the hospital or weather conditions.
3. To insure the proper preparation of the patient for safe anesthesia.
4. To assure constant physician attendance.
5. To maintain orderly hospital occupancy and economic utilization of nursing personnel.
6. To allow patients sufficient time to organize family responsibilities.

Since 1944 elective induction of labor has been performed by the Department of Obstetrics at the Worthington Clinic with increasing frequency and enthusiasm.[2] Originally the method was adopted because of shortage of beds, facilities, and physicians. A review of our results at regular intervals has encouraged us to pursue this method of delivery despite presently adequate hospital facilities, beds, and trained personnel. This paper is concerned with our experiences during the years 1961 and 1962.

TABLE 1

Groups	Below 20	20-30	31-40	Above 40
Spontaneous	42	246	77	6
Stimulated	15	74	26	4
Elective	18	204	81	6
Indicated	3	10	4	0
Cesarean Section	2	18	10	1

TABLE 2
Parity

Groups	0	1-4	5 or more
Spontaneous	99	239	33
Stimulated	28	78	13
Elective	39	234	36
Indicated	3	13	1
Cesarean Section	9	19	3

---

*Worthington Clinic.

TABLE 3
Duration of Labor
Parity

Group	0	1-4	5 or more
Spontaneous	9 hr. 42 min.	6 hr. 45 min.	4 hr. 22 min.
Elective	5 hr. 18 min.	3 hr. 0 min.	3 hr. 2 min.

TABLE 4
Apgar Ratings

Groups	10-7	6-4	3-0
Spontaneous	333	26	10
Stimulated	107	5	2
Elective	293	17	1
Indicated	10	3	2
Cesarean Section	20	9	0

TABLE 5
Weights by Weeks (EDC)
Elective Group

Weeks	# of cases	Av. Wt. (lbs.—oz.)
below 36	5	7 – 3
36	5	7 – 8
37	20	7 – 6½
38	72	7 – 8
39	75	7 – 9
40	68	7 –12
41	34	7 –13
42	9	7 –15
43	8	7 –13½
Undetermined	8	7 – 9

TABLE 6
Weight Comparison

Groups	Weeks by EDC		
	below 36	36-40	41 and over
Spontaneous	5-2½	7- 5½	7- 9
Elective	7-3	7-10	7-13½

Incidence

From January 1, 1961, to December 31, 1962, 847 patients were delivered at the Worthington Municipal Hospital. For analysis these patients were divided into five groups.

1. Spontaneous onset of labor.
2. Spontaneous onset of labor with stimulation.
3. Elective induction of labor.
4. Indicated induction of labor.
5. Cesarean section.

Only patients having obstetrical or medical indications for induction of labor were included in Group 4. Patients with spontaneous rupture of membranes without onset of contractions, who received intravenous syntocinon, were arbitrarily placed in Group 2.

Table 1 shows the number of patients in each group. In the two years of this study 309 labors (36.5%) were electively induced. In our previous study covering the years 1949-1953, 24% were electively induced. Eastman[3] reports an incidence as high as 25 to 35% in some of the best obstetric clinics. Private services run a consistently higher incidence than do ward services.

The patients in the various groups were distributed by age and parity as shown in Table 2. There were 36 grand multips electively induced. We agree with Ryan[4] and Blade[5] in England that when these inductions are performed by experienced obstetricians with ample personnel and facilities the risk to the mother and infant is less than in spontaneous labor. We do not believe a well engaged breech presentation contradicts elective induction.

Method and Selection

Elective induction of labor may be performed only when certain conditions are present:

1. A term-sized baby by menstrual history or clinical evaluation, an effaced cervix, and no disproportion.
2. The presenting part must be dipping into the birth canal.
3. The patient must be psychologically suitable and must not fear or object to induction.

Method of Induction

Our method of induction of labor as evolved over the years in some 9000 deliveries is as follows. The patient is scheduled for induction, is given a mild sedative to be taken the night before, and is admitted to the hospital at 7:00 A.M. in the fasting state. Following the routine admission procedures she is given a mild tranquilizer and a test dose of Syntocinon. A sterile amniotomy is performed, and a dilute solution of Sytocinon (10 minims in 500 cc. of 5% glucose in water) is given intravenously in sufficient concentration to initiate and maintain regular uterine contractions. A two-bottle setup is used. With close supervision the patient is then managed the same as any other patient in labor.

Results

Duration of Labor

The average duration of labor is compared between the elective and spontaneous groups on the basis of parity (Table 3). Of particular interest is the fact that the elective primipara delivered on the average in five hours and eighteen minutes, while the spontaneous averaged nine hours and forty-two minutes.

Condition of the Baby

A comparison of the Apgar ratings of the babies in the various groups is made in Table 4. The highest percentage of babies in the 7-10 Apgar group occurred in those electively induced.

Weights

Prematurity is one of the hazards of electively inducing labor. Estimation of fetal size by estimated day of confinement is not always reliable, and one must utilize clinical evaluation. Table 5 shows average weights in comparison to weeks of pregnancy by estimated day of confinement in the elective group. Although the majority of cases were 38 to 40 weeks, those above 40 and below 38 showed little difference in weight. There were 51 patients beyond 40 weeks, indicating that cervical effacement is of prime consideration in elective inductions.

TABLE 7
Premature Infants

Groups	# of Infants	%
Spontaneous	30 (22)	8.0
Stimulated	3 (3)	2.5
Elective	2 (2)	0.64
Indicated	2 (2)	11.0
Cesarean Sections	3 (1)	9.6
	40 (30)	4.7 Av.

* number in ( ) – survived

TABLE 8
Perinatal Mortality

Groups	Stillborn	Neonatal Death	Perinatal Mortality (#1.000)
Spontaneous	5	8	
Stimulated	2	0	
Elective	0	2	6.43
Indicated	2	1	
Cesarean Section	2	2	
			Av.– 27.9
State Av.			
Stillborn	12.4/1000		
Perinatal	28.9/1000		

TABLE 9
Hemorrhage

Groups	# pts.	Av. Blood Recd. (cc.)
Spontaneous	17	1235
Stimulated	6	916
Elective	8	1125
Indicated	3	1500
Cesarean Section	12	525

TABLE 10
Indications for Cesarean

Repeat	11
Bleeding	
Abruptio	2
Placenta Previa	3
Marginal Sinus	1
Cephalopelvic Disproportion (test of labor 6)	10
Other	
Diabetes	2
Cord Prolapse	1
*Face Presentation	1

When the elective and spontaneous groups are compared by weeks of gestation and weights the elective babies weighed more (Table 6).

In this group there were two infants premature by weight (5 lbs. 2 ounces and 5 lbs. 5 ounces), both of which survived (Table 7). The smallest baby (5 lbs. 2 ounces) was 40 weeks by estimated day of confinement. This is a prematurity rate of 0.64%. Stone[6] of New York reports a prematurity incidence of 4% in elective inductions. Our over-all incidence of prematurity was 4.7% compared to 9.9% in Stone's report.

Perinatal Mortality

Fetal salvage is the prime indicator of good obstetrical care. Ideally, elective induction should increase fetal salvage. In Table 8 the stillborns and neonatal deaths are listed for the five groups. There were 11 stillborns for an over-all rate of 12.7 per thousand births. The State of Minnesota average rate for stillborns for the same two-year period was 12.4. There were no stillborns in the elective group. There were two neonatal deaths in the elective group (both weighing over 2500 grams). Neither of these deaths as determined by the pediatricians was attributable to the induction. This is a perinatal death rate in the elective group of 6.43 per thousand. The State average was 28.9 per thousand. Our perinatal mortality for all groups was 27.9 per thousand. Hendricks[7] reports 37.2 per thousand for elective inductions at the University Hospitals of Cleveland during the years 1959 and 1960. All perinatal rates cited have been uncorrected.

Maternal Morbidity

A review of the groups showed no statistically significant difference in the morbidity rates. There were no maternal deaths. Postpartum hemorrhage has been cited by some authors as one of the hazards of the induction of labor. Table 9 lists the number of patients and average amount of blood given to the various groups.

Cesarean Sections

There were 31 Cesarean sections for an incidence of 3.6%; Table 10 shows the indications. There was one patient scheduled for elective induction who was noted to have a face presentation at the time of amniotomy. An attempt at conversion to vertex resulted in cord prolapse. A section was done and the baby survived. There were no sections done for toxemia, inertia, or Rh incompatibility. The two diabetic sections were repeats.

Comment

This review of our results with elective induction has supported our previous findings that with proper selection, standardized technique, and experience and good judgment the method is safe. We have been able to demonstrate a decrease in the length of labor and an increase in fetal salvage. Our rate of elective inductions points to a patient acceptance and confidence in the procedure. Our enthusiasm for elective induction still prevails.

Summary

1. A review of 847 consecutive deliveries is presented. These are divided into five groups.
2. Three hundred and nine or 36.5% of the cases were electively induced.
3. Comparison is made between the groups with emphasis on infant weights, duration of labor and fetal salvage.
4. Elective induction of labor is shown to be safe for the mother and even safer for the baby.

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7. et. cit. #3.

The Receding Chin

JOHN B. ERICH, M.D.*
Rochester, Minnesota

In contrast to retrusion of the chin accompanied by pronounced posterior displacement of the lower dental arch which presents a complicated problem in surgical repair, simple recession of the chin associated with relatively normal dental articulation is a deformity the correction of which is effective and uninvolved (Fig. 1 and 2). In posterior displacement of the mandible, the position of the lower jaw and teeth is such that an imperfection in facial contour is present; even when slight, the defect is always displeasing. However, simple recession of the chin, with which this paper is concerned, presents an external deformity that is more or less trivial. While this latter type of malformation usually is congenital, it may represent a residual defect that follows the correction of a class-II (lower teeth displaced posteriorly) malocclusion by orthodontic technics. In either case, a study of the patient's profile reveals a lack of harmony between the chin and mouth. The lower jaw seems to slope backward sufficiently to mar esthetically the outline of facial features. Although in these cases the imperfection in profile contour of the chin is admittedly inconsequential to the average observer, nevertheless, many stable and well-integrated persons with a receding chin are embarrassed, self-conscious, or sensitive about their deformity. The agreeable emotional changes which some of these people experience after a successful surgical repair of the defect offer convincing evidence that a receding chin can affect the personality adversely.

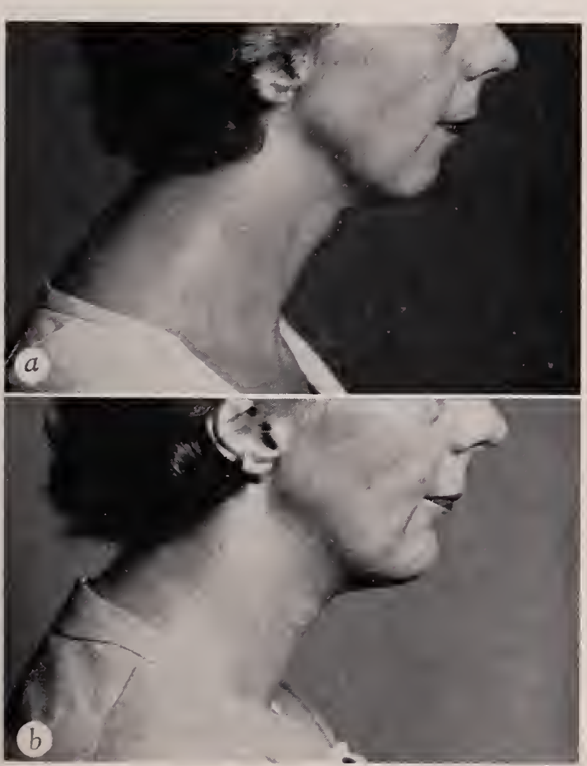

Fig. 1*a* — Receding chin. Preoperative profile view. *(b)* Postoperative profile view. Chin built up with cortical and cancellous bone from the crest of the ilium.

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*Section of Plastic Surgery, Mayo Clinic and Mayo Foundation.

Treatment

In contemplating treatment for simple recession of the chin, it is apparent that, since the teeth occlude normally, the problem is related not to maxillary function but entirely to esthetics. It is my opinion that the deformity can be corrected most easily by the use of a cortical bone graft and cancellous bone chips obtained from the crest of the ilium.

Obtaining the Graft

After adequate cleansing of the skin in the region of the anterior superior spine of one ilium, an incision that curves slightly downward is made in the skin along the iliac crest from the anterior superior spine backward for a distance of about six cm. Through this incision, the attachments of muscles and fascia are severed so as to expose about four or five cm. of the iliac crest. With a wide sharp chisel, the cortical bone over the crest is removed in one piece, after which a quantity of the underlying cancellous bone is scooped out with a gouge. All of the grafts are then placed in a sponge moistened with an isotonic solution of sodium chloride until they can be transferred to the region of the mandibular symphysis. To control bleeding at the donor site, a small piece of gelatin sponge (gelfoam) is inserted into the bony cavity. The overlying muscle and fascial tissues are approximated with chromic catgut stitches and the skin incision is closed with silk sutures. It is helpful to insert a small drain in the depths of the wound so that blood and serum can escape easily.

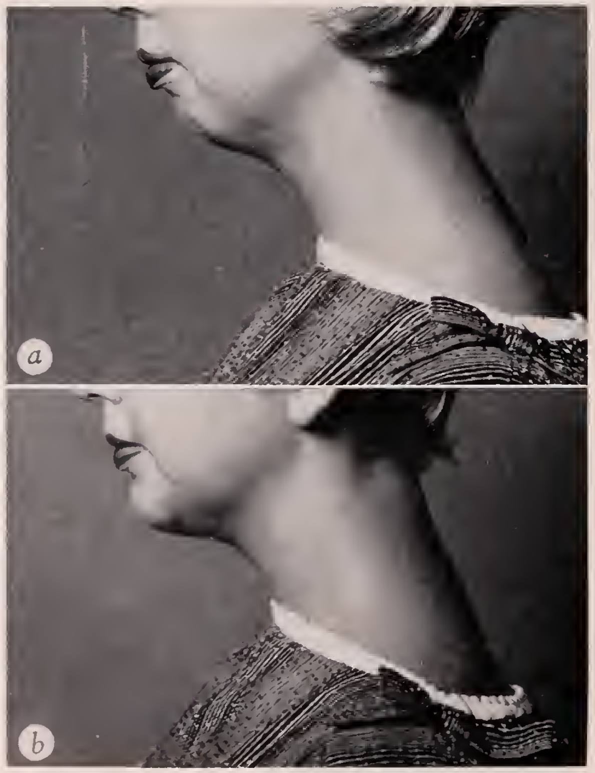

Fig. 2*a* — Receding chin. Preoperative profile view. *(b)* Postoperative profile view. Chin built up with cortical and cancellous bone from the crest of the ilium.

Exposing the Mandible

The skin of the lower lip and chin is thoroughly cleansed and draped with sterile towels. A small horizontal incision about two cm. long is made just to the right of the chin along the lower border of the mandible. Through this incision, the soft tissues over the symphysis of the mandible are separated from the underlying bone with dissecting scissors so as to leave a cavity over the anterior part of the mandible. In the preparation of this pocket, it is essential not to open into the oral cavity which would invite infection. Bleeding is controlled by external pressure.

Molding the Graft

The bone graft, which has cortical bone on one side and cancellous bone on the other, is evened up with rongeurs so that the width is uniform throughout its length; in addition, the ends are tapered. Two or three greenstick fractures are made by finger pressure on the cortical side of the implant, the fragments of which are not separated but hang together by means of the overlying periosteum. This piece of contoured and fractured bone is then easily bent to match the normal curve of the chin and is inserted through the external skin incision so that it covers the symphysis. In addition, pieces of cancellous bone which have been crushed by finger pressure into a pulp-like mass are introduced into the soft tissue cavity to cover the ends and convex surface of the cortical bone graft. The bony mass is easily molded with finger pressure to provide the desired contour for the chin.

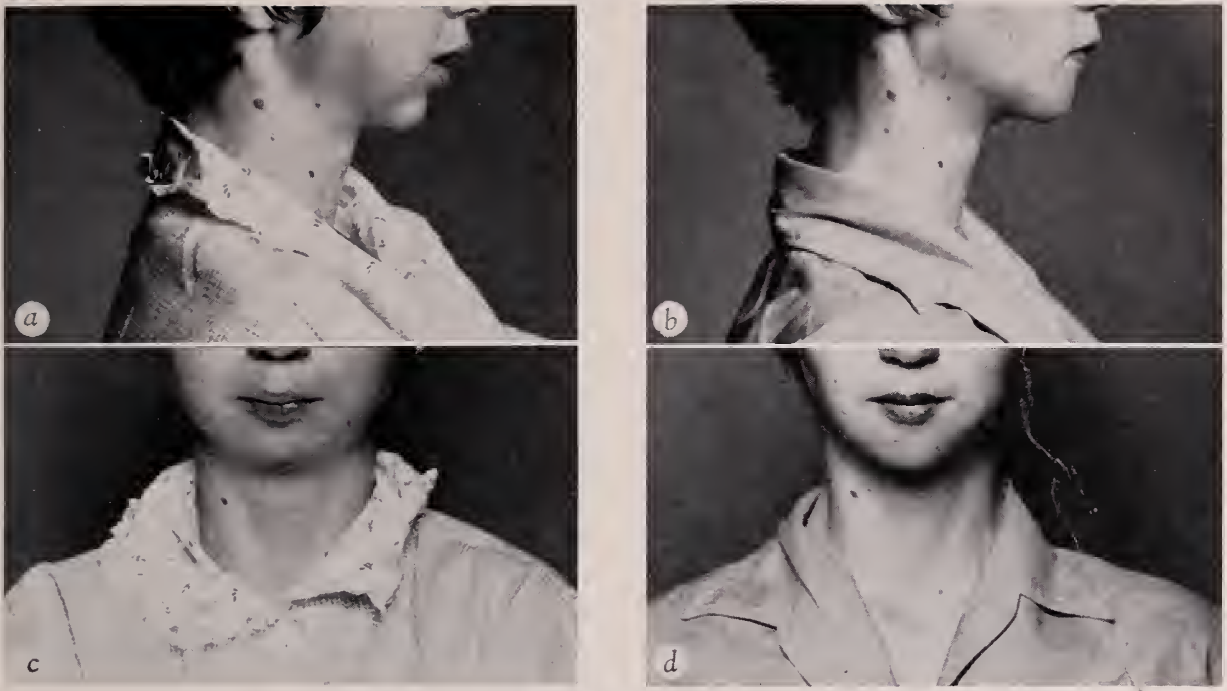

Fig. 3*a* — Receding chin. Preoperative profile view. *(b)* Postoperative profile view. *(c)* Preoperative front view. *(d)* Postoperative front view. Chin built up with cortical and cancellous bone from the crest of the ilium.

After suturing the small incision in the skin with fine silk, gauze is placed over the chin and many strips of adhesive tape are applied to immobilize the bone grafts in a desirable position. Within a matter of ten days, the transplanted bone forms a solid fixed mass. In my experience, the postoperative results in cases in which a segment of cortical iliac bone together with cancellous chips are employed are most satisfactory from an esthetic point of view, improving the contour of the chin not only of the profile view but also of the front view (Fig. 1, 2 and 3).

WHAT'S YOUR DIAGNOSIS?

Mr. J. B. was a thirty-two-year-old white male who was employed in the taconite industry. He was a heavy smoker. For as long as he could remember, even prior to his smoking, he had had a rather noticeable cough, often productive of a small amount of yellowish sputum. This had not changed appreciably. Multiple chest roentgenograms had been taken because of his employment. Apparently these had all been considered "normal," although several times a second X ray was taken.

While attending a baseball game, he felt chilly and coughed up a small amount of bright red blood. Over the next few hours he coughed up approximately a cupful of bright red blood. He had no elevation of temperature and other than feeling rather weak and nauseated because of his constant coughing, he had no other particular symptoms.

What is your diagnosis? Turn to page 926.

Take Time TO LAUGH — It is the music of the soul.

17-Ketosteroid
and
Volume of Human Urine*

Weekly and Other Changes with Low Frequency

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Minneapolis, Minnesota
CHRISTIAN HAMBURGER, M.D.**
Copenhagen, Denmark

CHANGES IN human 17-ketosteroid excretion with a frequency of one cycle per week were sought and found in an unusually long and reliable series of data. The analyses of a relatively large quantity of information were speedily and accurately accomplished by electronic computer. The physiologic changes detected by complex numerical operations are not readily apparent from inspection of the data. The changes may be called near-rhythms. Their regularity compares unfavorably with that of any well-known physiologic rhythm. The amplitude of these near-rhythms is small. Their statistical significance is high and their biologic importance is now amenable to study.

Background

A medical investigator has rigorously collected his 24-hour urines, with relatively few interruptions, for a number of years and has determined his daily 17-ketosteroid excretions according to his modification of the Callow procedure described elsewhere.[1] On the basis of the first six years' collection, he has reported[2] on a statistically significant annual rhythm in 17-ketosteroid excretion, with a crest in September (12.2 mg/day) and a trough in May (11.5 mg/day). He found further irregular day-to-day variations and changes with somewhat lower frequency in urinary 17-ketosteroid excretion.[2] A more detailed discussion of the frequency structure of this unusually long and reliable time series of endocrine interest was beyond the scope of the earlier report.[2] The day-to-day or week-to-week variability of the data on hand was great. Nonetheless, it was recognized ten years ago that such variability exceeded the limits of the technical variation.[2]

With the availability of modern electronic computer programs for the speedy evaluation of the frequency content of a time series, e.g., by variance spectra,[3-7] it seemed desirable to explore the possibility of certain rhythms or near-rhythms other than annual in the data evaluated earlier for seasonal variation.[2] We focused in a first set of analyses on possible components in a frequency domain extending from one cycle in a few days to one cycle in a month or one cycle in yet somewhat longer periods.

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*We are indebted for advice to Dr. Frank Unger, Associate Professor of Biochemistry, University of Minnesota Medical School, and to Dr. John Mason, Chief, Neuro-Endocrinology Division, Walter Reed Army Institute of Research, Washington, D. C. Mr. Frank Jones and Mrs. Marjorie Lindgren helped generously with the preparation of the data for computation. The study was supported by grants from the United States Public Health Service (5-K6-GM-13, 981; NB-04531-02; C-4359 C4), the American Cancer Society (E-155E) and NASA (Ns G-517).

**Department of Pathology, University of Minnesota Medical School, Minneapolis, Minnesota, Cambridge State School and Hospital Cambridge, Minnesota, and Hormone Department, Statens Seruminstitut, Copenhagen, Denmark.

Such analyses have already served one of us (FH) for the detection of an about-weekly spectral component in the body temperature behavior evaluated on a given individual longitudinally for long periods[7] — a source of variation recognized earlier by Kleitman and Ramsaroop.[8] A component with a similar frequency, among others, will be documented herein by pooled variance spectra for the excretion of 17-ketosteroids and the volume of urine of a healthy mature male.

Weekly hormonal changes can be viewed in the light of earlier work by Mason on monkeys, revealing lower urinary 17-hydroxycorticosteroid values on weekends.[9] Against this background, the analyses here discussed, based on data from a man, may be of interest at this time to the general and comparative endocrinologist or biologist, rather than to the classical clinical pathologist.

Apart from weekly changes, a near-rhythm with lower frequency in the 17-ketosteroid excretion of a healthy human male will also be shown to be statistically significant. Such findings broaden the scope of an already wide spectrum of frequencies now known to be exhibited by several body functions.[5-7,10-17] The question of the physiologic significance of these spectral components, however, must await additional analyses on added data, eventually from more than a single case.

Experimental Subject

A physically healthy subject is here under study during a period ranging from his 49th to 53rd year of life. He is an apparently normal and healthy married male, active as a medical investigator, as attested by a bibliography of 144 titles of scientific papers. He directs a state hormone laboratory and also practices medicine to a limited extent (e.g., consultations, injections, and prescriptions). He leads an unusually regular life and can be regarded as an extraordinarily well-balanced individual. Apart from this self-appraisal, consultations with others and the mere ability to follow through with thousands of urine collections on himself support the foregoing statement.

Mode of Life

The subject usually gets up spontaneously before 0700, on weekends and holidays as well as weekdays. An alarm-clock is set to wake him (for urine collection) at that clock hour when the need arises. Extremely rarely and only on Sundays or free Saturdays does the subject return to bed (after urine collection around 0700); but if he does, he probably will not sleep but read the newspaper, among other things.

The subject's daily schedule is usually the same on workdays, namely on Mondays to Fridays and alternate Saturdays. He reads newspapers from 0700-0815 and has breakfast from 0815 to 0830. From 0830 to 0915 he is in the bathroom, and invariably during this period he takes a hot shower followed by an "ice-cold" one. He rides a bicycle for about eight miles from his home to the laboratory, from 0915-1000.* Except for a ¾-hour lunch break, he is active in his laboratory from 1000 to 1700. During this period, research activity, routine work, administration and private practice require roughly 70%, 15%, 10% and 5% of his time, respectively. He takes no coffee or tea breaks. From 1700 to 1745 he rides home, again by bicycle. He has dinner and coffee from 1800 to 1900. Thereafter, until midnight his varied activities are about evenly divided between serious work and play, including study or relaxation by reading, woodcarving or oilpainting, chess and gardening. He retires between 0000 and 0030 and falls asleep within five to seven minutes, to wake up between 0615 and 0645.

The subject does not work on Sundays, his activities on this day varying greatly with the season. Early during the period covered by the data here analyzed (up to July 1954) the subject worked on Saturdays until about 1300 or 1400. Thereafter every other Saturday is comparable to a Sunday, while alternate Saturdays, like other days of the week, usually involve work in the laboratory from about 1000 to 1700. The circumstance that every other week the subject has two "Sundays" is of particular interest in that his fluid intake on such "Sundays" — including a bottle of beer at lunch and tea in the afternoon — exceeds that on weekdays by about 600 ml.

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*The fact that he switched to an automobile in December 1960, a timepoint subsequent to the period here analyzed, might be remembered for later analysis of added data.

On the average, on "Sundays" the subject is not exposed to most of the interruptions of a given activity by telephone calls, knocks on the door, conferences and other similar stimuli.

The subject smoked moderately during the period of study. He is not active in sports. His physical activity consists mostly of bicycling and gardening.

From October to April he exposes himself to a mercury quartz light; during the rest of the year he is in the sun whenever possible.

The subject's potentia generandi is attested by three healthy children. The potentia coeundi continued throughout the study period; the number of sexual outlets averaged about 100/year, corresponding activity being limited usually to the hours around midnight, except for mornings on weekends.

Collection of Urine

Urines are collected from 0700 of one day to 0700 of the next. One of the authors has strictly controlled the collection; he has been present at each of the thousands of times when the experimental subject emptied his bladder.

A given period of collection starts with an empty bladder. A sample of urine labeled for a given calendar day contains the excretion during seven hours of that particular day and that during 17 hours of the preceding day. The deadline of 0700 for collecting the last specimen of a given collection period is strictly observed. If it is surpassed by more than 10 minutes, a volume corresponding to the proportion of excess time is removed from the last voided specimen and added to the following collection.

Preservatives are never added to the urine. The specimens eventually are brought to a cooling room, maintained at +4°C and stored there in the dark until assay. However, one of us (CH) has stored samples of his urine at room temperature for years without detecting changes in 17-ketosteroid exceeding the limits of technical variation.

17-Ketosteroid Assay

The method used has been described earlier.[1,2] Consistently, the same technique is employed by the use of the same spectrophotometer in the same laboratory, even though the routine method of the laboratory has been modified and simplified in the course of the years.

Usually, batches of 10-18 samples are analyzed concomitantly for 17-ketosteroid. With each new batch, the last sample of the previous batch is reanalyzed.

General Comment on Variance Spectra

The procedure here used for computing a variance spectrum, also called a power spectrum, has been outlined elsewhere.[5,6] This method utilizes the technique of Tukey for the estimation of the statistical uncertainty of the spectral estimates.[3]

In the spectrum, a series of measurements made as a function of time, i.e., a time series, is viewed as the sum of a large number of sinusoidal functions with different periods. Half the square of the amplitude, plotted as a function of the reciprocal of the period, namely the frequency, is called the spectrum. The sum of all spectral values equals the total variance of the time series. The spectrum reveals the extent to which different "periods" or "frequencies" contribute to the variance of a time series.[18] The spectrum of a time series without rhythms is more or less horizontal. Rhythms or near-rhythms,[7] in turn, stand out as vertical bands of different widths in the spectrum. The more "regular" a rhythm, the narrower is the corresponding band in the spectrum. Broader bands characterize the less "regular" near-rhythms.[4-7]

Data Analyzed

The series of 24-hour urine volumes and 17-ketosteroid excretions available for the analyses here discussed stems from collections made between June 7, 1953, and August 2, 1957. Sections of this particular series, each consisting of consecutive daily values, are interrupted by several breaks of different duration.

Long breaks in the data result from omission of sampling during trips. Available data obtained during illness or those falling into periods when the subject studies the effect of hormone administration on himself are omitted from analysis, as are the periods immediately following such treatments.

The electronic computer program available for variance spectrum analysis at the time of this study is suited for the evaluation of data at equally-spaced intervals but is not applicable to values at unequal intervals. Therefore, sections of the total series consisting of uninterrupted consecutive daily values for urine volume and 17-ketosteroid are separately analyzed.

A first column in Table 1 lists the periods covered by the five longest available sections without major breaks, hereinafter named the "longer sections." The number of values in each of these longer sections is given in the second column of Table 1. This number includes interpolated values (see below).

Seven additional sections — hereinafter named the shorter sections — covering periods ranging from 22 to 53 days also are analyzed, though with lower resolutions. Additional, even smaller sections of data in the total series are completely omitted from these analyses.

TABLE I

Five Sections of Total Series, Each Consisting of Over 150 Consecutive Values for Urine Volume (V: in ml/24 hrs) and 17-Ketosteroid Excretion (KS: in mg/24 hrs)

			N of Interpolations	
Section No.	Period Analyzed (Month/Day/Year)	N of Values Analyzed	V	KS
1	6/ 7/53 - 11/19/53	166	2	2
2	11/28/53 - 11/12/54	350	5	5
3	11/24/54 - 7/ 8/55	227	3	4
4	7/20/55 - 1/25/56	189	6	6
5	8/17/56 - 2/24/57	192	0	0
TOTAL		1124	16	17

Interpolations

Short breaks stem, for instance, from breakage of glassware. For a missing datum in the middle of an otherwise uninterrupted section, a value corresponding to the mean of the preceding and the following value is interpolated.

The fourth and fifth columns in Table 1 indicate the number of interpolations for each of the five longer sections. These interpolated values are few in number (about 1½%) and probably of no consequence to the results. The shorter sections of 22 to 53 days are uninterrupted and hence without interpolations.

Program Used for Variance Spectra

The electronic computer program used for our purpose provides two types of "output," i.e., tables of exact spectral estimates as well as graphs of the rounded estimates. Such tables and plots are obtained, first, for separate uninterrupted sections of the total time series and, next, for the corresponding pooled spectrum.[19] These results are printed out automatically for each of the two physiologic functions studied, urine volume and 17-ketosteroid excretion. All of these outputs are obtained with several resolutions, i.e., with several m's. The m, determining the resolving power of the technique, is the number of lags to which an autocorrelation is computed, as the first step in spectral analysis.[5,6]

Graphs by Electronic Computer

For each of the spectra, at each resolution, two graphs are printed out (not shown). The abscissa of these graphs — representing frequency — is consistently linear in frequency, yet labeled in terms of period (reciprocal frequency). These abscissae cover a frequency domain ranging from one cycle in >112 days (left end of abscissae) to one cycle in two days (right end of the abscissae). The two types of graph differ in terms of their ordinate, which represents consistently variance per unit frequency. This ordinate, in each case, is plotted with a linear scale in a first graph and with a logarithmic scale in a second graph.

In the plot with a linear ordinate, each spectral estimate is marked by the height of a column of x's, as is illustrated in the bottom half of Figure 1, for urine volume. In this plot, the area under a portion of the line which could be drawn to connect the tops of the columns of x's approximates fairly the variance in the corresponding frequency domain.

The meaning of the area under the curve as an approximation of variance is lost in the graphs with logarithmic ordinates — on top of Figure 1, and in Figure 2, as a whole. In these plots, asterisks represent the spectral estimates, i.e., the variance corresponding to a given frequency analyzed.

The plot with a logarithmic ordinate has the property that small spectral variations are magnified when the spectral estimates are low. Small yet significant maxima then stand out clearly on these plots, since the 90% confidence limits of each spectral estimate also are indicated (in the plots with logarithmic ordinates) by the top and the bottom of a column of x's printed above and below a given asterisk.

Individual Versus Pooled Spectra

The separate variance spectra for each of the five longer sections of the total series do not show good agreement in terms of the location of their spectral components. The statistical significance of one or another component remains questionable on that basis. This point is illustrated in Table 2 for both urine volume and 17-ketosteroid excretion. This table lists only the location and rank order by height (in the spectrum as a whole) of components in the region of periods between four and 10 days.

At the bottom of Table 2, the location of the period of the weekly rhythm at seven

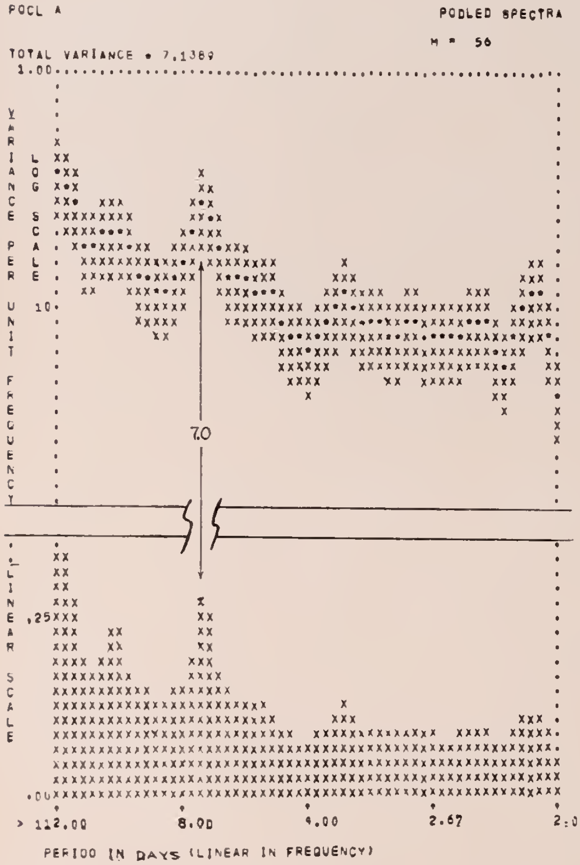

Fig. 1 — Summary of five sections of a time series on urine volume of a healthy, mature man, each section consisting of over 150 consecutive daily observations. Pooled variance spectrum with logarithmic ordinate on top. Corresponding summary with linear ordinate at the bottom. Arrow points to the estimates of a weekly near-rhythm (see text). N = 1124.

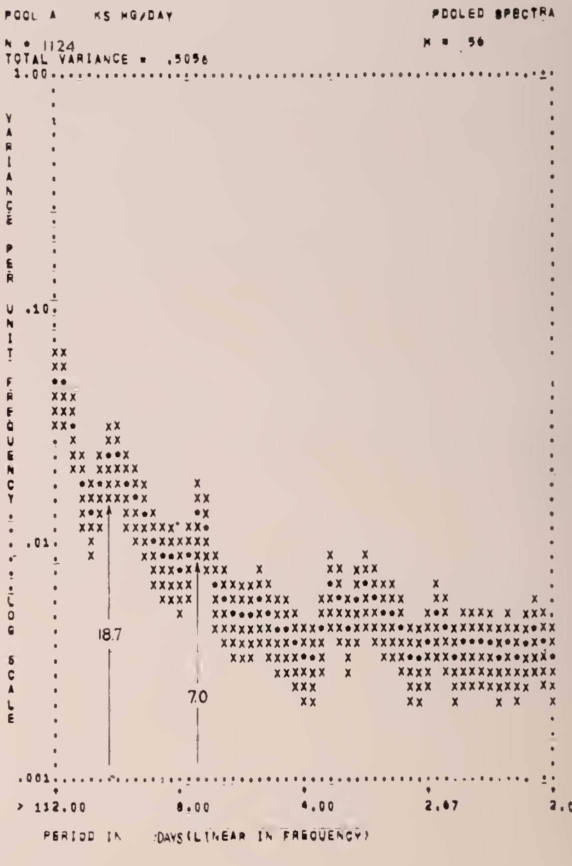

Fig. 2 — Pooled variance spectrum of five sections of a time series on 17-ketosteroid excretion of a healthy mature man. Arrows point to the estimate of a statistically significant about-weekly near-rhythm and to another yet higher maximum at about 19 days, awaiting further study (see text).

days is shown for both functions on the basis of a pooled variance spectrum. The statistical significance of the seven-day component has been ascertained for the pooled spectra in Figures 1 and 2, as will be amplified below. However, among individual spectra of the long sections, the location of the same component varies greatly and for one of these sections, this component is not even among the three highest spectral peaks.

Against the background of these results of individual spectra on the longer sections of data, the corresponding variable findings on the shorter sections are hardly surprising. Lower resolutions are used for these more limited data. For instance, with an m = 14, a seven-day component of 17-ketosteroid excretion is apparent in the spectrum of a data section covering 53 days. With similar resolution, individual spectra of four other shorter sections show a higher variance at the frequency of 9.3 days, but the statistical uncertainties associated with such estimates are great (large 90% confidence limits). Clearly, from an analytical statistical viewpoint the following discussion of the findings must be restricted to the results of pooled variance spectra of the 1124 observations constituting the five longer data sections.

The Weekly Near-Rhythm

In the pools of spectra with m = 56, summarizing the longer sections, a component with a period of seven days represents a broad band — for both functions, 17-ketosteroid excretion and urine volume. This weekly near-rhythm stands out above the general level of the spectrum. The plots with a linear ordinate visualize the about-weekly component best (only that for urine volume is shown at the bottom of Figure 1). The statistical significance of the weekly near-rhythm can be seen from the top half of Figure 1 for urine volume and for the excretion of 17-ketosteroids, in Figure 2.

The subject's routine, involving an increased fluid intake on "Sundays," must be kept in mind in viewing a weekly component of urine volume. The weekly change in 17-ketosteroid excretion is the more interesting component.

TABLE 2

Location of About-weekly "Peaks" in Individual and Pooled Spectra of Urine Volume (V) and 17-Ketosteroid Excretion (KS) in Sections of Data Described in Table I.

Data Section No.	"Period" in Days (Rank order) * V	KS
1.	4.9(3)	—
2.	6.6(3)	7.0(2)
3.	5.5(3)	4.3(3)
4.	7.0(1)	7.0(3)
5.	7.0(1)	7.0(3)
Pool:	7.0(2)	7.0(2)

* Numbers in parentheses indicate rank by height of a peak in the region from four to 10 days. Based on variance spectra resolving with m =56 a period domain from two to >112 days. Only three highest well-defined "peaks" in this domain are listed. The statistical significance of these "peaks" in sections of the data (see Table I) was not ascertained. Therefore, inferences, in this paper, will be based only upon the pooled data (bottom of table).

Spectral Components With Lower-than-Weekly Frequency

Apart from the weekly component, the low-frequency variance in the domain analyzed — from one cycle in two days to one cycle in over 112 days — is dominant over that with high frequency, in the spectra for both physiologic functions evaluated. This unequal distribution of variance along the frequency scale is more pronounced for 17-ketosteroid excretion than for urine volume, as can be seen by comparison of the two figures. In this connection, among other factors, the decrease in average annual 17-ketosteroid excretion, reported 10 years ago,[2] must be kept in mind.

A biweekly component in urine volume should be sought since every second Saturday corresponded to a "Sunday," in terms of fluid intake as well as in terms of the working routine. The linear plot of the pooled spectrum for urine volume in Figure 1 reveals indeed a secondary "maximum" corresponding to a period in the neighborhood of two weeks. However, the confidence limits of the corresponding estimates, plotted with a logarithmic ordinate on top of Figure 1, indicate that the statistical significance of the slightly longer than biweekly component in urine volume can not be verified by the analyses on hand.

In the pooled spectrum of 17-ketosteroid excretion in Figure 2, a component with a period of about 18 to 19 days compares favorably in prominence with the weekly near-rhythm. This maximum at about 19 days stands out significantly above the general level of the spectrum.

No attention should be paid to decimals indicated on the abscissa of the figure, e.g., in the case of the estimate at 18.7 days. Actually, the deviation from a period of 14 days, of the broad band around 19 days, will have to be examined by separate procedures, preferably in more extensive data, before this particular change in 17-ketosteroid excretion can be properly described as to its spectral location.

Time Relations Among Physiologic Functions

An earlier evaluation[2] of the relationship between urinary 17-ketosteroids and urine volume was based on 1880 samples. It should be noted in this connection, that in the earlier, more conventional analysis "no proportionality was found" between the excretion of 17-ketosteroids and the volume of urine,[2] except that in samples of urine below one liter there was a slight diminution of the average steroid excretion. Before re-examining temporal aspects of the same problem, the present analyses, based on restricted uninterrupted sections of the time series, will have to be complemented by a frequency analysis of the time series as a whole, with a computer program suitable for evaluating data at unequal intervals. Cross spectral analysis[7] might serve to rule out or to rule in a so-called coherence between urine volume and 17-ketosteroid excretion in the weekly and over-biweekly regions of the spectrum.

Significance of Weekly Near-Rhythms

Weekly change in human 17-ketosteroid excretion has a definite bearing upon the physiologic bases of work-rest routines. Menzel[16] has discussed the historical background of the custom of interposing among consecutive working days a full day of rest each week or so, as it has been adopted by several civilizations. The bearing of this custom upon work hygiene has also been justly emphasized by Menzel.[16] The same custom in our civilization involves on certain days, e.g., on "Sundays," a different level of stimulation of the adrenal cortex and perhaps of the testes, the two sources of urinary 17-ketosteroid.

Origin of 17-Ketosteroids

It is generally assumed that about ⅔ of the total 17-ketosteroids represent metabolites from adrenocortical steroids, the remainder originating from testicular steroids. Surgically castrated middle-aged male subjects were found[1] to excrete on the average the same amount of 17-ketosteroids as normal female subjects of comparable age. It is therefore reasonable to assume that the difference observed between the mean values of 17-ketosteroids in normal male and normal female subjects is mainly due to the testicular contribution. This difference, most marked in young and middle-aged subjects, gradually decreases from about 30 years of age on, as can be seen from Figure 3.[1]

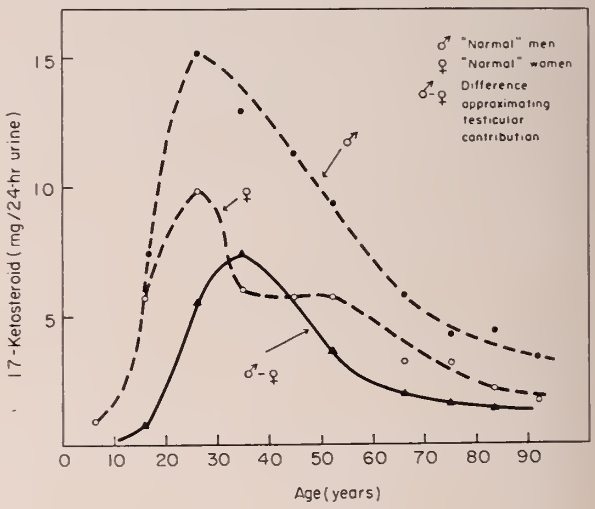

Fig. 3 — Human 17-ketosteroid excretion as a function of age in the two sexes, shown by broken lines, redrawn from Hamburger.[1] The continuous curve, representing the difference of the former two curves, visualizes the behavior with aging of the testicular contribution to the total 17-ketosteroid value.

The gradual decline in the testicular contribution to the 17-ketosteroids is also suggested by a comparison of the curves for the excretion of 17-ketosteroids and 17-ketogenic steroids (adrenocortical metabolites) as a function of age in both sexes. The reader interested in details of the age trends in steroid excretion can be referred to detailed data.[1,20-23]

The experimental subject's 17-ketosteroid excretion decreases by about one mg/24 hours during a six-year period ending at the time of the collections here analyzed and apparently remains at roughly the same overall level thereafter, until the time of this publication.

Steroid Excretion Following Emotional Loading

Stimuli that are disruptive of a given ongoing activity probably represent an emotional load. Inter alia, knocks at the door, telephone calls and conferences can generate such loads in our subject, and the load is lighter on "Sundays" as compared to workdays. The net effect of such loads may be a complex interaction of adrenal and testicular changes occurring partly in different directions in response to the same load. This possibility, though unproved for man, seems plausible in view of simian studies by Mason et al.[24]

These authors evaluated changes in hormone excretion repeatedly in two monkeys subjected to conditioned avoidance sessions of 72 hours' duration. Urinary 17-hydroxycorticosteroid levels showed about threefold elevations during avoidance and returned near baseline levels about six days afterward. Urinary androsterone, in turn, dropped to below half the baseline value during the period of an emotional load but showed substantial rebound elevations from three to six days following the avoidance session.

The findings of Mason et al. suggest that the direction and temporal relationships of these responses to the same stimuli are not the same. If similar differences in response of the adrenal cortex and the testes also characterize human behavior under minor and long-continued emotional loads, their net result might tend, at least initially, to dampen rather than to enhance a weekly change in total 17-ketosteroid excretion.

Earlier Work on Low-Frequency Changes in Human 17-Ketosteroid and Corticoid Excretion

De Pergola and Lonero have earlier reported on a "rhythm of seven days" in three of four healthy men and on a rhythm of 10 days in the fourth individual.[25] Their subjects, about 30 years of age, were younger than the subject of the present study. De Pergola and Lonero indicate further that they carried out daily determinations of 17-ketosteroids and 11-oxycorticoids for two months — a much shorter period than that investigated in our subject. A follow-up of this work, presented as an abstract,[25] will be of interest. Without data and/or reference to statistical analyses, however, the earlier work of De Pergola and Lonero cannot be compared with the analyses of the present data.

Weekly Near-Rhythm in Human Cortical Adrenal Function

The adrenal cortical contribution to the weekly component of the 17-ketosteroid spectrum might be more critical than the testicular contribution for several reasons. First, it seems reasonable to assume that the adrenal cortex of our subject probably contributes the larger share of the 17-ketosteroids. This contribution might be anticipated to be a larger proportion of the total value, in a middle-aged subject, as compared to younger men. Finally, the timing of the weekly change is pertinent. Additional analyses of our series reveal a lower 17-ketosteroid value on Sundays as compared to values obtained during the middle of the week, i.e., a lower value during periods of lesser emotional loads, with reduced reactive corticosteroid secretion.

The latter point, here considered for man, is particularly plausible in view of earlier studies by Mason on monkeys.[9] This author studied variations in mean urinary 17-hydroxycorticosteroid excretion as a function of the day of the week. His average values are based upon a total of 50 observations on five animals. These values expressed as mg/24 hours varied from 1.52 to 1.88, between Monday and Friday. The corresponding values for Saturday and Sunday were 1.16 and 1.17, respectively. During weekends, people were absent from the laboratory in which one monkey at a time was studied. The absence of human activities in the laboratory is appropriately noted by Mason as a factor underlying his simian results.

Some qualifications seem mandatory, however, at this point. Our results, though based on an unusually long series, describe only one individual with a certain mode of life. For human beings in general, it can be assumed only that the level of stimulation of the adrenal cortex will be different on days of rest or leisure activity, as compared to that on ordinary working days. Emotional and other loads conceivably could be higher rather than lower on weekends. They will vary, moreover, not only from person to person as a function of habit but also in the same person from time to time.

Only with the foregoing qualifications is the assumption warranted that a weekly near-rhythm in 17-ketosteroid excretion of a healthy man could represent, at least partly, a reactive phenomenon. This need not be, however, a full explanation. Much will depend on the issue as to whether about-weekly components persist in the absence of a weekly periodic change in the total environment. If so, the added question remains as to whether, e.g., on "self-selected" schedules, such near-rhythms exhibit a seven-day average period length or one that deviates from precisely that length.

General Discussion

The weekly changes here disclosed are of low amplitude, as revealed by subsequent analyses. These same studies,[26] however, have confirmed the high statistical significance of changes in 17-ketosteroid excretion with several frequencies, including those with one cycle in one week and those with one cycle in 17 to 21 days.

For an analysis of factors underlying about-weekly physiologic near-rhythms, the data requirement is large. The search for a significant deviation of their average period from precisely seven days is of interest by analogy to results of similar work on many circadian (about 24-hour) rhythms. Incidentally, the latter work is facilitated by the higher amplitude and greater regularity of circadian steroidal rhythms as compared to those with lower frequency here described.

Circadian Rhythm

It is now well established that in the absence of a known environmental synchronizing input with a corresponding frequency or after removal of the receptor for such synchronization[27] certain circadian rhythms exhibit an average period length that deviates consistently from exactly 24 hours. Such non-24-hour circadian rhythms, exhibited by many organisms and functions, have no known exact environmental counterpart. In frequency terms, such results indicate circadian desynchronization.

Desynchronization

By analogy, the possibility of desynchronization of an about-weekly near-rhythm from a weekly environmental schedule also must be considered. However, the observation that in the analyses of some sections of the present series on 17-ketosteroid excretion and urine volume the "period" of the about-weekly spectral component differs from exactly seven days is not necessarily pertinent. Moreover, the extent of this "deviation" varies among sections (Table 2). With the considerable "noise level" on hand, even the longer sections of data analyzed individually are too short for a definitive interpretation of precise period lengths in the about-weekly domain. The same consideration conceivably applies to other studies.[25]

The statistical significance of changes such as those reported as a 10-day rhythm[25] as yet does not seem to be ascertained. The possibility remains that random sampling error contributes to such inferences from limited data.

Tasks for Future Work

Studies of organisms on "random" and non-weekly cyclic routines, among other well-specified conditions, will be needed, in any event, to explore more rigorously the question as to whether about-weekly components result, at least in part, from the organism's intrinsic functional integration, quite apart from the probable amenability of such near-rhythms to synchronization by precise weekly and, perhaps, by other environmental routines.

If one wishes to compare the behavior of the about-weekly physiologic changes to that of the much more prominent circadian rhythm,[7] one should also raise the question as to the extent to which an about-weekly spectral component might prove to be amenable to frequency synchronization with different near-weekly environmental cycles, as well as with a precise seven-day routine, and, also, as to whether this component persists on "self-selected" routines as well as on "random" or "constant" ones, as far as the realization of the latter is feasible.

Summary and Conclusions

Extensive bionumerical analyses, applied by the use of an electronic computer to data on steroid excretion, provide new quantitative, so-called spectral, endpoints — hopefully of interest to those concerned with evaluating the role of steroids in biology and medicine.

The material studied consists of a series of 17-ketosteroid determinations on 24-hour urines collected rigorously for several years. This series of determinations was started in 1947, at a time when steroid chemistry had not advanced to its current sophistication. If a similar series would be started in the 60s — as has been done in the Department of Pathology at the University of Minnesota — more extensive and more specific steroid determinations could have been analyzed by the use of the techniques here demonstrated and others developed in the interim.[26]

In any event, sections of an exceptional time series, consisting of consecutive values for the 24-hour excretion of 17-ketosteroid and urine volume of a healthy, middle-aged man, analyzed by variance spectra, reveal statistically significant changes of several frequencies in both physiologic functions.

An about-weekly change in urine volume relates to the subject's known increased fluid intake on weekends. A component with a frequency of one cycle per week in the spectrum of 17-ketosteroid excretion is the more interesting. A second prominent peak around 19 days in the spectrum of the 17-ketosteroid excretion of an adult human male also is demonstrated.

Despite their small amplitude, the weekly and other lower-frequency changes here disclosed for human 17-ketosteroid excretion are statistically highly significant. For a more complete evaluation of these near-rhythms, it will be important, eventually, to segregate the contribution of adrenal and testicular steroids.

The basic questions can now be raised as to whether about-weekly and other lower-frequency components in a spectrum of physiologic rhythms are simply "impressed from without" in health and whether they are related to and, if so, exaggerated in prominence by certain diseases that are associated with a similar temporal pattern in their symptoms.[13,28] For this purpose, the behavior (possible persistence?) of an about-weekly period in the absence of a weekly environmental routine deserves study in the several functions, such as 17-ketosteroids and body temperature, for which an about-weekly near-rhythm has now been repeatedly detected and documented in the absence of obvious illness.[7] In the context of such questions of experimental pathology and physiology, this demonstration of significant weekly hormonal changes relates further to problems of work hygiene.

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10-28 will be in the reprints or may be obtained from the author.

To lengthen thy life, lessen thy meals.—Benjamin Franklin

IT'S THE LAW

Permitting Office Girl to Treat Patient is Evidence of Doctor's Negligence

Evidence that a doctor permitted his office girl, a high school graduate with two years' experience as a nurses' aide, to treat a patient's lacerated hand on at least twelve occasions was held sufficient to send to the jury the question of the doctor's negligence, even in the absence of expert testimony. Accordingly, the Massachusetts Supreme Court overturned a lower court's directed verdict for the doctor.

The patient had consulted the doctor after injuring his hand at work. The doctor bathed the hand, gave penicillin and antitetanus injections, and prescribed medication for relief of pain.

When the patient returned to the doctor's office two days later, he was treated by the doctor's office assistant, who removed the bandage, soaked and bathed the hand, and rebandaged it. She instructed the patient to return to the office two days later. He did so and was treated by the doctor, who found that the thumb was swollen and that the flesh around the stitches was swollen and infected.

For more than a month the patient continued treatment, visiting the doctor's office a total of seventeen times. On no more than four of the visits was he seen by the doctor, being treated on the other occasions by the office assistant. She removed stitches, squeezed pus out of the thumb, prescribed pills, injected penicillin, removed and reapplied bandages, even advised the patient as to the treatment to be followed.

In the patient's suit against the doctor for malpractice, there was no expert testimony that the doctor was negligent in his treatment of the patient. However, the court said that there was sufficient evidence from which the jury could have found that the doctor did not use his best judgment in order to produce a good result. One basis for such a finding was the patient's testimony that the doctor failed to prescribe hospitalization, even after it was clear that the patient's thumb was infected. Another basis was the action of the doctor in permitting the patient to be treated by his office assistant to the extent described. The court concluded that the jury would be warranted in finding, without the aid of expert opinion, that the doctor's treatment of the patient was not consistent with standard medical practice.

Delaney v. Rosenthall, 196 N. E. 2d 878 (Mass., March 4, 1964)

ANSWER TO WHAT'S YOUR DIAGNOSIS

(From page 915)

Bronchiectasis is one of the most common causes of hemoptysis. Although there are multiple other possibilities, this would be considered first with this history.

Praise

Is our oldest human relations tool (praise) really a psychological piece of candy?

—Harvard Business Review

Politician: An animal who can sit on a fence and yet keep both ears to the ground.

—Anonymous

Cerebral Palsy

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CEREBRAL PALSY is the principal disease causing crippling in children. The purpose of this paper is to focus attention on three main aspects of this condition: etiology, incidence, and orthopedic treatment.

Etiologic Factors

Concerning etiology, the term cerebral palsy implies a paralytic state resulting from cerebral damage of any nature. Common usage, however, restricts the term to cases in which the paralysis has existed from birth or early life, thereby excluding such conditions as cerebral vascular accidents of later life.[1] Progressive diseases such as brain tumors and tuberous sclerosis that produce peripheral manifestations are also excluded.

All forms of cerebral palsy are the result of anomaly, injury, or disease of the brain, a part of the body in which the functions are so diverse as to allow for an infinite variety of disturbances. This damage of the brain produces a related defect of motor power and co-ordination which in turn may result in a variety of clinical syndromes: spasticity, athetosis, rigidity, tremor, and ataxia. These can be differentiated as follows.

Clinical Syndromes

Spasticity is marked by hyperirritability and hypercontractility of a muscle when it is stretched. It is determined by the presence of an exaggerated stretch reflex, increased tendon reflexes, an extensor plantar response (Babinski), clonus, and contractures.

Athetosis is an abnormal amount and type of involuntary motion, usually slow and writhing in nature. It may be more easily thought of as an involuntary attempt to assume a position or to move a joint in a certain way, rather than an involuntary stimulation of any individual muscle. It is characterized by normal tendon reflexes, a flexor plantar response, and absence of the stretch reflex.

Rigidity is a hypertonic resistance to movement throughout the entire range with normal or decreased tendon reflexes, a flexor plantar response, no exaggerated stretch reflex, and no clonus.

Tremor is a rapid, rhythmic, repetitive pattern of motion.

Ataxia is a disturbance of balance and equilibrium of cerebellar origin.

The difficulty with this classification is that these syndromes are rarely found in a "pure" clinical picture. For example, spasticity is frequently mixed with athetosis or rigidity.

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Some clarity may be obtained by thinking of these as anatomic syndromes. In general, it may be stated that lesions of the motor cortex, basically of the upper motor neuron, result in loss of normal inhibition of the lower motor neuron and thus uncontrolled spasticity of the involved muscles. This is the opposite of the situation in anterior poliomyelitis, in which damage of the lower motor neuron results in flaccid muscles. Lesions of the base of the brain, or basal ganglion, result in dyskinesias, that is, athetosis, rigidity, and tremors. Damage to the cerebellum causes ataxia and inco-ordination and is instrumental in producing poor muscle tone.

Anatomic Syndromes

Thus we are concerned with three anatomic syndromes; cortical, ganglionic, and cerebellar.

The Cortical Syndrome

The cortical syndrome, which accounts for 50 per cent of all cases of cerebral palsy, produces a paralytic state, usually spasticity. Not all muscles, however, become spastic; some may be weak, normal, or flaccid, the change, if any, depending on the location of the lesion. If the lesion is in area 4 (somatic motor), flaccidity will result, usually in spotty distribution since the pyramidal tract has a facilitative function. However, one rarely encounters a pure pyramidal tract lesion, because the damage is not so sharply localized. The usual and more predominant damage is to area 6 (premotor area), which is the cortical area of flexor inhibition; with this inhibition lost, spasticity results.[2]

If the lesion is located toward the vertex of the motor area, chiefly the legs are involved; if the disturbance is lower in the motor area, the arms may be affected. A small lesion in an isolated area would result in monoplegia; a larger lesion restricted to one hemisphere would produce hemiplegia. A lesion in the area of longitudinal fissure, which would involve both hemispheres, would result in paraplegia; and if the lesion were extensive enough on one side to involve also the arm area, a triplegia would exist. A quadriplegia would be a double hemiplegia. The often misquoted term "spastic diplegia," or Little's disease, in which the lower extremities are spastic in extension and adduction, is in reality a paraplegia.

The Ganglionic Syndrome

Basalar syndromes make up approximately 40 per cent of all cases of cerebral palsy. Since the basal ganglion has a variety of functions, lesions in this area could produce a large combination of syndromes. There is usually gross dyskinesia with some form of athetosis, rigidity, or tremor.

The Cerebellar Syndrome

Cerebellar syndromes account for the remaining 10 per cent and are manifested by ataxia.

Here again, these anatomic syndromes may be pure or mixed, in any combination, the type depending on the location and extent of the lesions in the cortex, basal ganglion, and cerebellum. In addition, they may be confused by accompanying and associated findings of mental deficiency, convulsion, or impairment of speech, sight, or hearing.

Intellectual Capacity

A lowered capacity for intellectual activity is perhaps the greatest limiting factor in the clinical picture outside of purely motor manifestations. This impairment may be genuine or only simulated, because of lack of education or training. Of those patients judged feebleminded, a small portion will be normal mentally but retarded because of a physical handicap. At least 15 per cent of palsied children are so deficient in intellectual capacity as to render futile any attempt at habilitation.

Thirty to 40 per cent of cerebral-palsied children have convulsive episodes. Most of these are grand mal; occasionally some are jacksonian; petit mal and psychogenic episodes are rare. The use of braces and the performance of reconstructive surgery in these cases require special care.[2]

Disturbances of speech are common and may even be a contraindication to surgical treatment.[3] Impairment or loss of sight or hearing is less common, but when present it can seriously impair therapy.

Pathologic Changes

The majority can be categorized as developmental, traumatic, or infectious, and the usual end result is cerebral anoxia or hemorrhage.[4] When we then ask what causes this damage, the nature of cerebral palsy emerges. Cerebral palsy is a well-defined entity with a variety of causes and pathologic changes.[4] It is difficult to distinguish fact from theory and cause from effect; handicaps of a physical or mental nature cannot easily be separated, for one affects the other.[5] In most cases the exact cause is never precisely determined but only surmised. The best way to approach the individual case is by the history, as the causative factors can thus be listed chronologically with birth as a reference point. The major causes are as follows:

Prenatal Disorders

Prenatal disorders may arise from conception to onset of labor. This accounts for 20 per cent of total cases.

Hereditary influences, with genetically transmitted developmental defects in the basic nuclei or their tracts (or both), for example, familial spastic paraplegias (1 per cent of total).

Normal variation in structure and function, for example, infolding of various anlages or clefts of the motor cortex.

Congenital anomalies, for example, cerebral atrophy.

Acquired disorder in utero. The majority of prenatal causes lie here.

a. Infection, usually neurotropic virus acting on the brain, for example, measles, toxoplasmosis, and syphilis.
b. Cerebral anoxia caused by interference of oxygen flow through the placenta or cord.
c. Cerebral hemorrhage, for example, after trauma.[6,7]
d. Kernicterus: a special category. The toxicity of bilirubin for brain tissue is the chief mechanism for brain damage. The majority of cases manifest as athetosis. There are many causes, of which erythroblastosis fetalis is the most frequent, previously accounting for 10 per cent of all cerebral palsy. However, this incidence has been reduced to 1 to 2 per cent by prompt care.
e. Metabolic disturbances, for example, toxemias of pregnancy and diabetes mellitus.
f. Fetal irradiation.

Paranatal Disturbances

Disturbances occurring during parturition account for 70 per cent of total cases.

Trauma and vascular damage.

a. Prolonged labor. A prolonged difficult labor is traumatic, as is a precipitous delivery with sudden change of intracranial pressure.
b. Physical injury from delivery, for example, laceration of cortex, depressed fracture, and subdural hematoma. Naturally, high-forceps, breech, and mid-forceps deliveries are fraught with much danger, but it is interesting to note that spontaneous delivery is more often damaging than low-forceps delivery with episiotomy.[4]

Conditions that produce anoxia.

a. Mechanical respiratory obstruction (asphyxia).
b. Narcotism, with depression of fetal respiratory center, for example, overdose of drugs or prolonged anesthesia to the mother during delivery.
c. Placental and cord abnormalities.
d. Maternal anoxia or hypotension.
e. Conditions immediately after birth, for example, convulsions, fever, and drowsiness with decreased respiration.

Of these natal factors, three points are worth noting. First, premature and postmature babies are more prone to all the dangers noted above and therefore show a higher incidence of cerebral palsy.[4] Second, obstetric judgment must be exercised to prevent prolonged labor and traumatic delivery. However, in a statistical study[8] it was impossible to blame "poor obstetrics" for more than 3 per cent of cases of cerebral palsy due to birth injury. The other causes are unavoidable. Third, the terms "birth palsy" and "cerebral palsy" are not synonymous.

Postnatal

Damage in this group from birth to five years of age is easiest to determine, since the child was normal before a specific event. It accounts for 10 per cent of the total cases.

Traumatic injuries, for example, trauma to the head, brain contusions, and skull fractures.

Infections, for example, meningitis, encephalitis (13 per cent of total in one series),[3] pertussis, and brain abscess.

Toxicity, for example, by lead, arsenic, and coal-tar derivatives.

Vascular accidents, for example, hemorrhage and emboli.

Anoxia, for example, strangulation and CO_2 poisoning.

Sequelae of intracranial surgery.

Incidence

Cerebral palsy is the most common of the neuromuscular crippling diseases. Poliomyelitis is the second most common; it has a variable incidence from year to year, but over-all is less common than cerebral palsy. In some years the incidence of poliomyelitis exceeds that of cerebral palsy; but in other years it is far less and should diminish even more with the widespread use of Salk and Sabin vaccines. No other causes of crippling disease in children approach either of these two in frequency.

Phelps[9] stated that "cerebral palsy seems mainly a human condition, since its occurrence in any of the animals, even the anthropoids, is exceedingly rare." The sex ratio is about even, with slight preponderance in males (55 per cent males, 45 per cent females).[8] There is no class or economic status in which the condition is more prevalent than in any other.

Cerebral palsy, unlike poliomyelitis, is an accurately predictable disease, both in overall incidence and incidence in each classification. In cerebral palsy the problem is the same for each 100,000 population, whether city or rural area. Seven persons per 100,000 population are born each year with cerebral palsy. One of these seven will die in infancy. This leaves a practical case load of six. Two will have such serious impairment of their intellectual facilities that any program of effective training would not be feasible; they will require permanent custodial care. One will be so severely handicapped physically that habilitation from the viewpoint of self-help or locomotion is questionable. Two will be moderately handicapped and capable of great improvement; with proper therapy in all spheres of their problem, these patients can achieve some degree of useful and happy life. The final one of the seven will have mild disability and often will make a satisfactory adjustment in ordinary surroundings. Since the life expectancy of patients with cerebral palsy is nearly that of normal persons, the total number of cases can be accurately calculated.[9]

TABLE I
Extent of Involvement in Various Series of Cases of Cerebral Palsy
(Figures are Percentages)

	Phelps[9]	Lipscomb[8]	Brockway[8]	McCarroll[10]
Quadriplegia	57.2	56.0	28	27
Hemiplegia	21.9	20.9	32.4	39
Paraplegia	11.8	14.9	28	25
Arm				0
Leg				25
Triplegia	7.5	2.3	1.8	6
Monoplegia	1.6	5.9	8.6	3
Arm				0.7
Leg				2.3

Amenable to Habilitation

Of the seven patients, the two who are moderately handicapped and mentally normal present the chief problem; they are the ones who can be helped most. Since the first 20 years of life is the optimal time for intensive therapy, there would be 40 such cases in each 100,000 population or 400 cases in each million. In the United States, then, there would be approximately 72,000 (400 x 180) cerebral-palsied persons who are mentally normal, who have handicaps of moderate degree, who are under 20 years of age, and who are thus amenable to sufficient habilitation to afford them a definite place in the social and economic world.

Of the cortical or spastic group, the extent of involvement can best be shown in the review of various series in the table.

The predominant lesion is seen to be quadriplegia. It is interesting to note that Mc Carroll,[10] in 1459 cases of spasticity, found no cases of paraplegia of the arms. From the discussion of etiology, it will be recalled that this would require two separate lesions, one in each hemisphere.

The percentage of total cases of cerebral palsy amenable to surgical treatment is given by various authors as 15.7 per cent,[8] 16 per cent,[11] 16.7 per cent,[12] and 26 per cent.[10] The percentage suitable for surgery would depend upon the type of institution. Those which have patients under observation for prolonged periods would be in a better position to advise operative treatment.

Treatment

The goals of treatment in cerebral palsy are (1) to prevent deformity, (2) to correct and relieve deformity already developed, (3) to improve function (by conservative as well as by active surgical means), and (4) to achieve as full a degree of habilitation or rehabilitation as possible.[5] The ultimate aim of therapy, then, is to help each patient develop the highest degree of independence and normalcy possible for him.[13]

Since the defects of cerebral palsy are so diverse, the treatment of necessity takes many forms. Clinics and special cerebral palsy hospitals have been developed, and the group or team approach has become the standard. Thus nearly every medical specialty is called upon at some time during the patient's life.

Orthopedic treatment in cerebral palsy consists of the administration of drugs; the use of physical therapy, splints, and braces; and surgery.

Drug therapy is mentioned in passing as an adjunct to produce sedation and relaxation, and to control seizures; these factors are particularly important in preoperative and postoperative care.

Physical Therapy

The function of physical therapy is to teach the fundamental motion of one joint. These motions can later be grouped. For the patient with spastic disability, repetitive methods of muscle training and voluntary exercises to strengthen the weak antagonists are of definite value. Passive exercises should be avoided since they are defeated by the stretch reflex. Substitution and adaptation of the intact cortex is encouraged early by simple active exercises, the skilled motions being postponed until late in the treatment.[8] In cerebral palsy of basalar origin, voluntary motion is present; the aim of therapy is to overcome the involuntary motion characterized by athetosis, rigidity, and tremor. These disappear on relaxation and sleep. Relaxation is consciously acquired or is induced by massage in a suitable environment. Thus, as voluntary motions are abolished, purposeful and co-ordinated motions are acquired. For proper relaxation, a calm, quiet atmosphere is necessary. For ataxia the treatment is simply that of training the voluntary motor centers to take over the function of damaged mechanism.[9]

Prosthetic Appliances

Tendon stretching in plaster wedge boots will appreciably reduce the number of patients who require surgical treatment.[14] The application of splints as a trial before operations to fix joints is often a guide to the result that may be expected.[15] Braces may be used alone or in conjunction with surgery.

Most writers believe that braces have a definite place in the prevention of contractures.[5,13,14] Barnett[15] expressed the belief that deformities in growing children, whether they are caused by spasms or by contractures, should not be operated on unless braces are to be applied postoperatively to prevent recurrence of the deformity.

As noted previously, approximately 16 per cent of all the cerebral palsied undergo one or more surgical procedures at some time or another. This figure will undoubtedly increase as methods are improved and indications are broadened. Even though the gain achieved by surgical treatment in cerebral palsy is often distressingly small, properly selected procedures should be performed to minimize uncontrolled spasticity or tension which interferes with the restoration or improvement of ambulation.

Surgery

Ninety to 95 per cent of all operations in cerebral palsy are performed on the spastic child.[4] The old teaching, "Never undertake surgery for athetosis," is slowly being revised, so that elimination of tension and its resultant overflow and deformities in the patient with tension athetosis is being realized in selected cases.[16] Rigidity also can be benefited. Orthopedic surgery still has no place in cases of tremor and ataxia, though it may have in the future.[5] Thus, in the main, it is for the spastic form of cerebral palsy that the greatest surgical efforts have been made.

Of the operations devised, present thinking seems to favor stabilization procedures, tendon lengthening or transplant, and neurectomies, alone or in combination.[10,17-19] It goes without saying that each surgical procedure should be adapted to the individual case.[8]

Most authors agree that the main causes of poor results are (1) failure to assess properly the whole deformity, (2) inadequate or overcorrection of the deformity, and (3) failure to maintain correction by prolonged use of splints, braces, and physiotherapy.

A successful surgical operation depends not only on the surgeon's technical ability and the patient's intelligence, but also on the determination of the patient to improve.[5]

Summary

Cerebral palsy has been presented from aspects of etiology, incidence, and treatment. We should remember that the disease is always of intracranial origin and that we are treating the effect, not the cause. The very nature of the condition is such that we will probably always be confronted with the problem. Cerebral palsy is a predictable phenomenon; we can plan ahead to provide facilities and care for its multiple manifestations.

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Pliny's* Treatment for Eye Disorders

For the cure of cataract, it is recommended to apply a wolf's excrements reduced to ashes and mixed with Attic honey. Bear's gall, too, is similarly employed; also goat's gall with honey and one-third part of white hellebore** is used for cataracts.

For the cure of epinyctis, wild boar's lard, mixed with oil of roses, is thought to be very useful.

For affections of the eyebrows and for diseases of the eyelids and corners of the eyes, beef marrow from the right foreleg, beaten up with soot, is employed.

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*See Minnesota Medicine June, 1964, Page 716.

DEAD FETUS SYNDROME

(Fibrinogen-fibrin Conversion Syndrome)

Prolonged intrauterine retention of a dead fetus is associated with hemorrhage of incoagulable blood. Persistent tachycardia is a constant feature of this syndrome. Frank hemorrhage seldom occurs until the fibrinogen value drops to 90 mg. per 100 cc. or less.

In this condition the pregnancy should be interrupted by amniotomy or hysterectomy depending upon the clinical circumstances. It is preferable to provide transfusion or the administration of fibrinogen before terminating a pregnancy, and the date of termination should be pronounced when the fibrinogen blood value begins to fall below 150 mg. per 100 cc.

Durham, Paul B. Hoeber, Inc.
Encyclopaedia of Medical Syndromes
New York

Kanavel's Sign

(Tenosynovitis of ulnar Bursa)

This is a point of maximum tenderness over the ulnar bursa of the palm, proximal to the distal flexion crease, in the hypothenar eminence. Exquisite tenderness in this area indicates tenosynovitis of the ulnar bursa.

Liberty

They that give up essential liberty to obtain a little temporary safety deserve neither liberty nor safety.—Benjamin Franklin

Pyloric Stenosis

- with
- Hematemesis
- and
- Jaundice

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PYLORIC STENOSIS is not an uncommon condition. During the past twelve months six babies (four male, two female) have had surgery for pyloric stenosis at the Naeve Hospital in Albert Lea. The incidence for pyloric stenosis varies from two to four cases per one thousand live births, depending on the locality. According to Wallergren the incidence in Sweden for live births is one in one hundred fifty in boys and one in seven hundred seventy-five in girls. Both hematemesis and jaundice are symptoms rarely associated with pyloric stenosis. The present case report is unusual in that these symptoms are associated together with pyloric stenosis in a four-week-old female.

Case Report

The patient was born in Albert Lea on December 18, 1962, after eight months gestation. The pregnancy had been complicated by bleeding during the fourth month and the mother was treated with enovid. The delivery was normal and birth weight was 5 pounds, 14 ounces. The mother's blood was O Rh negative. The baby was also Rh negative and the Coombs' test was negative. The neonatal course was normal except for slight jaundice noted on the fourth day. The baby was discharged on the sixth day weighing 5 pounds, 7½ ounces. She did well on a standard formula except for a decrease in the amount taken at each feeding after the third week. Mixed cereal and vitamin drops had been started only one day before admission.

Onset of Symptoms

At exactly one month of age the baby was admitted, having had several tarry emeses during the previous six-hour period. Two of the emeses were definitely positive for blood by hematest. The stools were scanty and of normal color. There was no fever.

Physical Findings

The baby was mildly lethargic but not dehydrated. The temperature was normal. The weight was 6 pounds, 6 ounces. The abdomen was moderately distended and the liver was palpated two centimeters below the right costal margin. There was no icterus noted initially. The hemoglobin was 15.1 gm.%; hematocrit 44%; white blood count 23,100 with 9 stabs., 28 segs., 61 lymphs; urine negative. The initial diagnosis was neonatal sepsis.

Initial Treatment

After blood cultures were taken, the baby was treated with penicillin and streptomycin. A spinal puncture obtained clear fluid containing no cells. Subsequently the blood and spinal fluid cultures were negative. On the day after admission there was continuous emesis, although the material did not contain blood. Definite clinical jaundice was noted. A total bilirubin was 12 mg.%. Although the baby was only mildly dehydrated, intravenous fluids were started. A repeat bilirubin after about six hours was 6.65 mg.% total with 5.58 indirect and .07 direct-acting bilirubin. The serum transaminase was 50 SGOT units, the thymol turbidity 0.2 units. A repeat hemoglobin was 13.5 gm., and white blood count 12,000 with 1 basophil, 3 eosinophils, 11 stabs., 31 segs., 54 lymphs. There were no nucleated red blood cells.

Progress

On the second day after admission the baby continued to vomit even after very small feedings of dextrose water. An X ray of the abdomen showed a stomach bubble with almost no gas in the remainder of the abdomen. An upper gastrointestinal X ray showed a dilated stomach which retained the contrast material and a string sign in the pyloric area.

On the third day a definite pyloric tumor could be palpated. An attempt was made to give thickened feedings with atropine, but the vomiting continued. By the fourth day the jaundice had completely disappeared. Surgery was done on this day and a dilated stomach with a large pyloric tumor was found. A conventional Fredet-Ramstedt procedure was done. The baby tolerated this well and had an uneventful postoperative course. She was discharged one week after surgery, weighing 6 pounds, 12 ounces. At the present time she is well and has shown no evidence of hypothyroidism, galactosemia, hemolytic disease, defect in bilirubin metabolism, or biliary atresia.

Comment

Pyloric stenosis is mentioned as a rare cause of hematemesis in Shaffer's book, DISEASES OF THE NEWBORN.[1] It is thought to be due to gastric dilatation with rupture of small submucosal vessels and most often occurs after very forceful emesis. It is unusual that tarry emesis was the presenting symptom in the present case.

The time at which jaundice appears in the infant is very important when one considers the differential diagnosis. According to Shaffer,[1] jaundice which first appears more than four days after birth cannot be due to hemolytic disease of the newborn. Physiologic jaundice generally disappears by the end of the first week but may persist into the second week, especially in prematures. Only in rare instances does physiologic jaundice last for four weeks. When jaundice appears after the fourth day, sepsis neonatorum should be seriously considered as well as hereditary spherocytosis. In patients with galactosemia, jaundice characteristically appears between the fourth and eighth days of life.

Intranatally or postnatally-acquired viral and protozoal infections must be considered as well as bacterial infections. Neonatal hepatitis cannot be ignored, since its onset may take place at any time from birth to four months. If bilirubinemia is pronounced and the bilirubin is almost all indirect, yet without evidence of increased hemolysis, it is justifiable to think seriously of congenital familial nonhemolytic jaundice. Diagnostic possibilities for obstructive jaundice (usually in patients with over 35% direct acting bilirubin) include: (1) inspissated bile syndrome (following erythroblastosis, other hemolytic anemias, or neonatal hepatitis), and (2) anatomic obstructions such as atresia of the bile ducts, choledochus cyst or, more rarely, cystic fibrosis of the pancreas, enlarged periportal glands, or neoplasms.

Jaundice due to pyloric stenosis was first reported in the United States in 1955 by Martin and Siebenthal.[2] They reported on two male infants — one five weeks and the other seven weeks of age. Their cases were treated surgically and in both the pylorus was described as angulated posteriorly and laterally around the gastrohepatic ligament in such a way as to cause compression of the common bile duct. A bilirubin level was obtained in only one of their cases. The total bilirubin was 17.3 mg.%, of which only 1.6 mg. was direct. Mechanical obstruction due to pressure on the common bile duct is an easy explanation for the jaundice, but the bilirubin in these cases has been predominantly indirect.

In 1959 Arias, Schorr, and Fraad[3] reported the case of a four-week-old male, in whom the bilirubin reached 18 mg.%, of which 13.1 mg.% was indirect. Their studies included a liver biopsy, which contained a marked decrease in activity of glucuronyl transferase, the enzyme necessary to conjugate bilirubin.

In 1962 Nakai and Margaretten[4] reviewed two hundred twenty-seven infants with pyloric stenosis and found five with jaundice that could not be explained by other recognized causes of hyperbilirubinemia. They noted in their cases that the bilirubin was indirect and liver biopsy showed no evidence of bile stasis. These authors suggest that the jaundice may be due to underprofusion of the liver as a result of increased intra-abdominal pressure from gastric dilatation of pyloric stenosis, pressure causing portal vein obstruction rather than extra-hepatic duct obstruction. In commenting upon this article in the YEARBOOK OF PEDIATRICS 1962-1963,[5] Doctor Audrey Brown does not agree with this explanation and states that a total loss of portal blood flow does not significantly impair bilirubin metabolism in experimental animals and that hyperbilirubenemia is not a prominent consequence after portacaval shunt in humans.

The pattern of jaundice with pyloric stenosis is so varied that it is unlikely that only one mechanism is involved. It seems more likely that a combination of factors including dehydration, undernutrition, deficient enzymes, and pressure on the portal vein or common duct may be responsible for jaundice with pyloric stenosis.

Summary

Hematemesis and jaundice may be early symptoms of pyloric stenosis.

Acknowledgment

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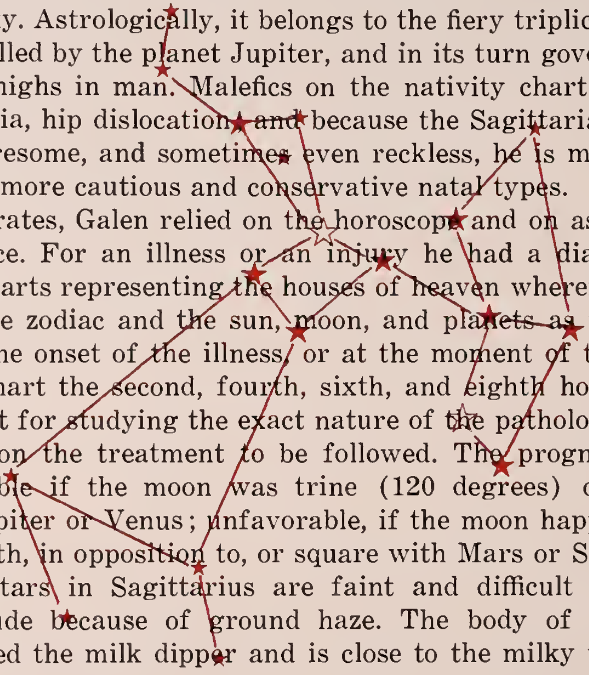
Astrology and Medicine — Sagittarius



Sagittarius, the Archer, sun sign from November 22 to December 22, is radiantly visible during August at mid-evening as it arcs its way across the southern sky. Astrologically, it belongs to the fiery triplicity of zodiacal signs, is controlled by the planet Jupiter, and in its turn governs primarily the hips and thighs in man. Malefics on the nativity chart predispose to sciatica, coxalgia, hip dislocation, and because the Sagittarian is apt to be restless, venturesome, and sometimes even reckless, he is more subject to fractures than more cautious and conservative natal types.

Like Hippocrates, Galen relied on the horoscope and on astrology in his medical practice. For an illness or an injury he had a diagram charted with 12 equal parts representing the houses of heaven wherein were placed the signs of the zodiac and the sun, moon, and planets as they appeared in the sky at the onset of the illness, or at the moment of the injury. On this nativity chart the second, fourth, sixth, and eighth houses were the most significant for studying the exact nature of the pathology in question and resolving on the treatment to be followed. The prognosis was considered favorable if the moon was trine (120 degrees) or sextile (60 degrees) to Jupiter or Venus; unfavorable, if the moon happened to be in conjunction with, in opposition to, or square with Mars or Saturn.

The lower stars in Sagittarius are faint and difficult to see in the northern latitude because of ground haze. The body of Sagittarius is sometimes called the milk dipper and is close to the milky way. The bow is pointed toward Scorpion intent upon killing to avenge Orion's death.

We cry loudly for a man of vision and when we get one we call him a visionary.

*Acetophenetidin**

Fatal Renal Disease Due To Long-Term Overingestion

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In 1953 Spühler and Zollinger published an extensive review on chronic interstitial nephritis[1], in which they noted incidentally that 14 of their 44 patients gave a history of the excessive use of headache preparations. They raised the question as to whether this might be a cause of the renal disease or whether it merely reflected an attempt to gain relief from the headache often accompanying chronic uremia.

Since this first report there has been a virtual flood of papers in European literature, principally from the Scandinavian countries and Switzerland, as well as reports from Australia and South Africa describing chronic interstitial nephritis and renal papillary necrosis in association with the long-term overuse of acetophenetidin.[2,3] There has even been a symposium devoted to the subject.[4] Moeschlin[5] maintains that habituation to this drug is one of the commonest toxicomanias in Europe, being exceeded only by alcoholism and nicotinism. Surprisingly enough, although the per capita consumption of acetophenetidin is said to be as high in the United States as in Switzerland,[6] a thorough search of the literature reveals that only 26 cases of renal toxicity produced by this drug have been reported in the American literature,[7,8,9,10,11,12,13,14,15,15a] all since 1960. Two of our leading pharmacology texts make the statement that this drug does not impair renal function.[16,17]

Since the outcome in these patients is so frequently fatal, it would seem that the problem needs more widespread attention in this country. Hence the following case is reported in detail. The patient was a 31-year-old female who took the drug for the relief of headaches related to previous central nervous system disease. She was under close medical supervision most of her life and had never had evidence of pyelonephritis or other specific renal disease. She was known to have had adequate renal function as recently as one year prior to the time she entered the hospital and died in renal failure.

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*From the Department of Medicine, University of Minnesota Hospitals.

Case History

This was the sixth admission of a 31-year-old white housewife, who was brought to the hospital by her husband on December 10, 1962, with the complaint that she had become progressively somnolent and hard to arouse over the preceding three days.

Past History

At age three the patient had suffered an episode of head trauma followed by four hours of unconsciousness, and soon afterward began to have petit mal seizures. At age 12 she was admitted to another hospital in status epilepticus and from that time on she was troubled with frequent right-sided Jacksonian seizures.

She was first seen at University Hospitals in 1955 for further evaluation of her seizures, which were poorly controlled with large doses of anticonvulsants. At that time a review of symptoms revealed a complaint of frontal headaches for many years, usually relieved by aspirin. The electroencephalogram demonstrated a left temporal spike focus.

Previous Surgery

Craniotomy was done and a seizure focus located by electrocortiography. The anterior six cm. of the left temporal lobe was resected.

The patient appeared to benefit from her surgery. She was followed frequently in the Outpatient Clinic where she had a large variety of nonspecific complaints and a constant complaint of marked increase in the severity of her headaches which were variably described as originating in the left frontoparietal area or the left occipital area.

Previous Medication

She was given a variety of analgesics and sedatives with varying efficacy, the most constantly prescribed medication being some form of APC either plain or in combination with other drugs. Questioning of her husband revealed that she had been taking large amounts of a proprietary form of APC tablets for her constant headaches for some six to eight years; over the past year her rate of consumption had increased to an average of 100 tablets per week. A 100-tablet bottle purchased four days prior to admission had been found empty the day she was brought to the hospital.

Other Illnesses

Other history revealed an apparent hemorrhagic diathesis. She had bled heavily at the time of several operations which included a craniotomy, a cesarean section, and a gastrectomy, done because of a massive upper gastrointestinal hemorrhage. She complained of metrorrhagia and had had a post-partum hemorrhage after the birth of her second child in 1955. A low grade anemia of 10-11 gm. per 100 ml. had been documented over the past two years, dating from about the beginning of her last pregnancy, during which time she had had a serum Fe of 37 mcgm. per 100 ml.

Retrospective Evaluation

Retrospectively the patient's chart from this hospital as well as charts from two other hospitals, where she had been followed at frequent intervals as far back as 1944, were reviewed carefully for evidences of other types of renal disease. Her numerous complaints at clinic visits included abdominal and back pain and on rare occasions brief periods of frequency or nocturia. Many urinalyses were recorded and intermittently trace or + albuminuria was reported, including frequent examinations during pregnancies. An occasional examiner commented on costovertebral angle tenderness, but urine cultures at these times were consistently sterile. She had had three pregnancies, bearing living children in 1955, 1958, and 1961. With each of her last two pregnancies a diagnosis of pre-eclampsia was made at term, but this was on the basis of blood pressures of 130/80-90 mm. Hg, a trace of + albuminuria, and a trace of ankle edema on one occasion. Recorded urea nitrogen determinations included 17 mg. per 100 ml. in 1955, 8 mg. per 100 ml. in 1957, and 18 mg. per 100 ml. in 1961. Sedimentation rates were consistently low, perhaps because of her chronic salicylate use.

Physical Findings

Physical examination revealed a thin, apparently chronically ill, dusky-skinned, somnolent female. She was easily wakened but promptly fell back to sleep. When awake she asked repeatedly for a proprietary analgesic compound which contains 3.25 gr. acetylsalicylic acid, 3.0 gr. acetophenetidin, and 0.35 gr. caffeine per tablet. Vital signs were normal. Her respirations were deep and slow but not Kussmaul. The skin was dry and lacked turgor. There were many one-to-six-cm. ecchymoses over her lower legs. The lungs were clear. A grade 2/6 systolic murmur was heard at the base. Examination of the abdomen revealed no tenderness and there was no costovertebral angle tenderness. Neurologic examination was within normal limits except for the state of consciousness. Pelvic examination revealed a dark, bloody cervical discharge.

Laboratory Data

Admission laboratory data showed a hemoglobin of 10.5 gm. per 100 ml. and a white-cell count of 13,800 with 92 per cent neutrophils. Urinalysis revealed a specific gravity of 1.015, pH of 5, a + test for albumin, occasional red and white cells and a negative nitroprusside reaction for ketones, with a positive ferric chloride reaction for salicylates. The blood sugar was 139 mg., urea nitrogen 109 mg., and serum salicylate 45 mg. per 100 ml. Electrolyte determinations included a sodium of 137 milliequiv., a potassium of 4 milliequiv., a chloride of 101 milliequiv., and a carbon dioxide combining power of 4 milliequiv. per liter. An arterial blood pH was 7.24 with a pC02 of 13 mm. Hg and a bicarbonate of 5 milliequiv. per liter.

The Treatment

A diagnosis of acute salicylate intoxication was made and the patient was started on intravenous fluid and sodium lactate therapy. Since her last urea nitrogen determination 14 months earlier had been normal at 18 mg. per 100 ml., her uremia was felt to be prerenal in origin secondary to her dehydration.

Progress

The patient quickly improved clinically and her urine output ranged between one and two liters per 24 hours. The serum salicylate fell and the blood gas determinations returned towards normal. However, with hydration the hemoglobin dropped to 7.1 gm. and the urea nitrogen remained above 100 mg. per 100 ml.

Chronic Toxicity

Further studies at this time revealed a creatinine clearance of 5.3 L per 24 hours, with serum creatinines of 10.3 and 11.1 mg. and a uric acid of 13.2 mg. per 100 ml. Hematologic studies included normal prothrombin time, bleeding time and clotting time, and normal red-cell indices. Blood methemoglobin concentration was 0.22 gm. and the serum Fe was 35 mcgm. per 100 ml. with a reticulocyte count of 4.4 per cent. Serum bilirubin was 0.1 mg. and 0.4 mg. per 100 ml. one minute and total respectively. The bone marrow was normocellular showing some premature segmentation of neutrophils and megakaryocytes and an increased amount of storage iron. It was felt that this patient's hematologic and renal picture was consistent with chronic acetophenetidin toxicity.

Pyuria

On the third hospital day she developed abdominal pain, pyuria and left costovertebral angle tenderness. Microscopic examination of unspun urine revealed many Gram-negative rods (she had previously been catheterized with difficulty and had had an indwelling catheter for two days), and tetracycline was started. Culture subsequently grew out greater than 100,000 colonies per cc. of E. coli. Bilateral retrograde pyelography was performed on separate days, revealing kidneys that appeared to be of normal size and shape with normal pelvicocalyceal systems. Transfusion to a hemoglobin of 10.4 gm. per 100 ml. was carried out.

Renal Failure

Despite substantial urine outputs the urea nitrogen began to climb slowly (Fig. 1). On the ninth hospital day it had reached a value of 188 mg. and the potassium was 4.5 milliequiv. per 100 ml. It was decided to dialyze the patient; this was carried out without event.

Shock

The following morning the patient suddenly went into shock. Laboratory data at this time included a hemoglobin of 18.4 gm. per 100 ml. and a white count of 44,200 with 93 per cent neutrophils. Fluid shifts secondary to the dialysis or Gram-negative septicemia were considered. Blood cultures drawn at this time were subsequently negative. The blood pressure responded nicely to plasma infusion, but the patient became oliguric and the urea nitrogen again rose (Fig. 1). Hyperkalemia was managed for a time with exchange resins. With a rise in the urea nitrogen to 156 mg. and the potassium to 7.1 milliequiv. per 100 ml. with marked electrocardiographic changes of hyperkalemia the patient was dialyzed a second time.

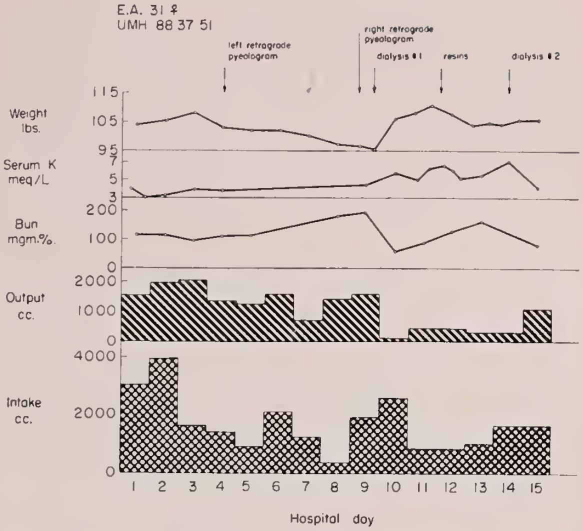

Fig. 1 — Hospital course of the patient.

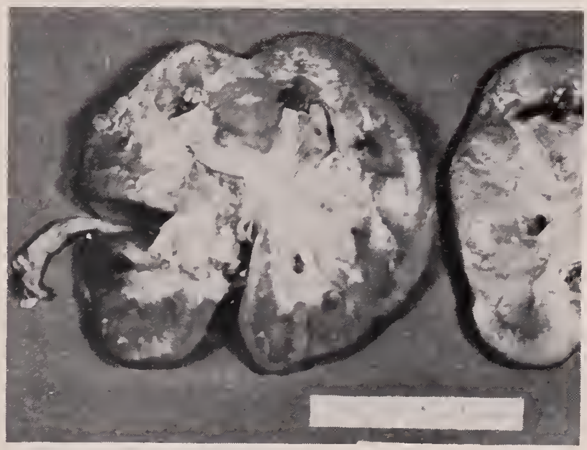

Fig. 2 — Cut surface of the kidneys showing necrosis of every papilla.

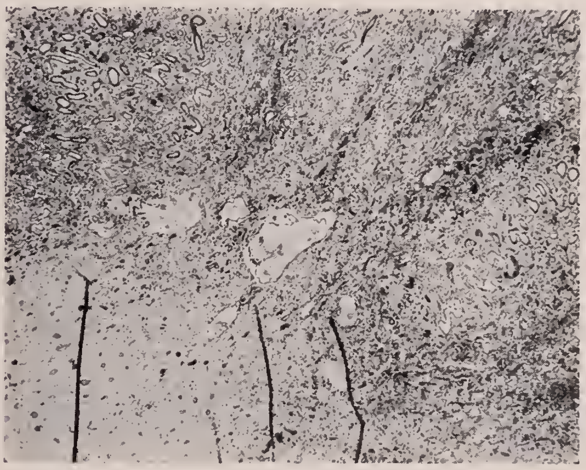

Fig. 3 — Microscopic appearance of tissue from deep in the medulla. The lower left hand corner shows an area of papillary necrosis while areas of interstitial infiltration are prominent in the rest of the section.

Death

Following the second dialysis there was a fall of the potassium to 4.2 milliequiv. per 100 ml. and a marked rise in the urine output. However on the 16th hospital day she had a grand mal seizure and cardiac arrest. Attempts at resuscitation were unsuccessful.

Autopsy Findings

At autopsy there was 500 cc. of bloody fluid in the peritoneal cavity and marked necrosis of the pancreas. The liver showed evidence of some ischemic damage. The spleen was enlarged and congested. The brain was somewhat smaller than expected and the tip of the left temporal lobe was absent, with the defect showing cystic degeneration. Sectioning showed encephalomalacia extending from the defect to the anterior limb of the internal capsule with the basal ganglia on the left also involved. The other organs and tissues were normal with the exception of the kidneys.

The Kidneys

The right kidney weighed 110 gm. and the left 140 gm. The surface of the kidneys was smooth with no fine scarring, but linear depressed areas of the cortex did impart a grossly lobulated appearance. The cut surface had a striking appearance with every one of the papillae being black and necrotic (Fig. 2).

Pathology

The Papillae

Microscopically (Fig. 3) the most noteworthy change was in the papillae. The tip of each papilla was involved in a coagulative type of necrotic process with a lack of cellular detail but an over-all semblance of the original architecture. These necrotic areas stained very lightly with eosin, and there was no evidence of differential nuclear-cytoplasmic staining. The margins of the necrotic areas were slightly irregular, and there was no increased inflammatory response in the junctional area. No abscesses or granulomata were seen.

The Cortex

The depressed regions of the cortex exhibited a marked amount of interstitial fibrosis with resultant compression and atrophy of the tubules. The interstitium was diffusely and densely infiltrated with inflammatory cells, chiefly lymphocytes and plasma cells, with an occasional polymorphonuclear leucocyte. In these areas of scarring marked thickening of the tubular basement membranes was noted. A small number of the glomeruli in the areas of atrophy were completely hyalinized, and some of the remaining glomeruli showed scarring of the tufts and marked capsular fibrosis which was strikingly demonstrated with Masson's trichrome and the periodic-acid-Schiff stains.

The Tubules

The majority of the tubules in the areas not involved by the scarring showed varying degrees of dilatation with flattening of the lining epithelium. Interspersed among these were a few normal-appearing tubules and a small number of tubules which exhibited slight hydropic degeneration. The Masson's trichrome and periodic-acid-Schiff stains showed some thickening of Bowman's capsules in these areas but no significant alteration of the majority of the tubular basement membranes. Many of the connecting tubules in the medullary area were filled with hyaline debris and desquamated cells.

Macrophage-like cells containing a golden-brown granular pigment were noted in many of the Bowman's spaces and in the lumens of some of the tubules, with a similar pigment seen in a few of the tubular epithelial cells. This material gave a negative reaction with the potassium-ferrocyanide hydrochloric acid stain for iron but was strongly Schiff-positive with the periodic-acid-Schiff stain.

The Blood Vessels

The vasculature showed varying amounts of fibrous intimal thickening. This was most severe in the areas of scarring, but moderate degrees were also noted in the medium-sized arteries in other regions.

Discussion

This woman's course was comparable to the other reported cases of this disorder. Her intake of acetophenetidin containing compounds had been large, constant and prolonged. It is particularly significant that there was present a cause other than chronic renal disease for her headaches extending back almost to childhood. Her past history was documented in detail with no evidence of other forms of renal disease. Her renal disease was essentially silent and was not discovered until her last admission.

Headache

Her continued complaint of headache was no doubt in large part a manifestation of toxicity to the drug (see below). This drove her to consume more and more of the medication until she was taking enough pills to get acute salicylate intoxication in addition to her other lesion. Her profound acidosis was probably due in large part to her severe kidney disease, which was coupled with the metabolic acidosis common to salicylate intoxication. The pathologic picture of a nonpitted surface, severe papillary necrosis, damaged tubules surrounded by collagen and diffuse interstitial inflammatory change, and relatively normal glomeruli and blood vessels corresponds to that described by others.[1,2,3,7,12,14,18,19] The significance of the pigment contained within macrophages seen in this case is unknown. Moolten and Smith[7] and Reynolds and Edmondson[14] described a similar pigment in their studies, but it gave a positive reaction for iron.

Toxicity of Acetophenetidin

The hematologic toxicity of chronic acetophenetidin ingestion has been known for some time. The manifestations include methemoglobinemia, sulfhemoglobinemia, a low grade hemolytic anemia with Heinz bodies in the erythrocytes, as well as leukocytosis and a bleeding tendency.[16,17] A blue-gray coloration of the skin due to the abnormal heme pigments is often noted. Habituation to the drug is frequent, due to its pecular property of producing severe headache when taken in large doses. Associated nervousness, irritability, depression, tremor, weakness and mental debility lead to the ingestion of more drug for the relief of these resultant symptoms.[5,7,16] This differs from true addiction in that taking the drug, rather than its withdrawal, creates the condition compelling its use.[7,17] Only in the last decade, following a substantial increase in the consumption of this drug since the Second World War, has this more serious toxicity of kidney damage been recognized.

Renal Insufficiency

The literature on acetophenetidin abuse and renal insufficiency has been recently reviewed by several authors;[2,3] therefore an extensive further review will not be given here. Schreiner[2] raises the question of why there are so few reports of this type of toxicity in the American literature and maintains a cautious skepticism with respect to any cause and effect relationship. Ross[3] feels that one can conclude that acetophenetidin does cause renal damage on the basis of the following evidence:

1. A large proportion of acetophenetidin habitues show evidence of renal damage,
2. A large proportion of patients with interstitial nephritis or papillary necrosis give a history of prolonged acetophenetidin ingestion,
3. In general the severity of the renal lesion is greater when larger amounts of the drug have been taken, and
4. There is considerable improvement in the renal disease after withdrawal of the drug.

In answer to the question of Spuhler and Zollinger[1] as to whether the abuse of analgesics may not be a consequence of pre-existing renal disease, Ross[3] cites the fact that these patients have headaches for a long period of time without other symptoms of renal disease, as did this patient, and notes that the renal disease is frequently seen when the drug is taken for other reasons, e.g., arthritis. Although many analgesic combinations have been associated with renal insufficiency, acetophenetidin is the only common component of all of them. Ross grants that the most important argument against an association is the fact that the kidney lesion has not yet been produced in experimental animals by giving them large amounts of the drug. However, he points out that these experiments were all done in rodents, which metabolize this compound differently than humans, and no experiment has involved an exposure of more than two years. Other drug toxicities seen in man cannot always be reproduced in animals. He feels that chemical toxicity is the most likely pathogenetic mechanism.

Bacterial Influence

Although most workers feel that this is an abacterial disease, Spühler[18] believes this lesion is not caused by acetophenetidin per se but is a specific variety of bacterial infection of the kidneys superimposed on underlying damage caused by the drug. It is known that the kidney is frequently exposed to bacterial seeding in healthy people. Spühler feels that bacterial invasion of the kidneys probably occurs frequently but results in actual renal infection only infrequently. If the kidney had previously been damaged it would be less capable of resisting infection, even by bacteria of low virulence.

Early Symptoms

Unfortunately it is difficult to detect this disease early because there are few complaints and these are nonspecific. Anemia is a common presenting feature. One should question any patient with unexplained renal impairment or urinary tract infection about use of the drug, and it should not be given to patients with a past or present urinary tract abnormality.[3,12,14] An Addis count may show red and white cells without casts. The specific gravity of the morning urine is low. There may or may not be bacteriuria. An intravenous pyelogram may show decreased concentrating ability and papillary necrosis.[3] The latter should also be identifiable by retrograde pyelography. In one reported case tissue was found in the urine, twice associated with flank pain. This was identified microscopically as a renal pyramid.[11]

Colombi[20] feels it is possible to distinguish clinically between chronic interstitial nephritis and chronic pyelonephritis on the basis of the absence or rarity of back pain, bacteriuria, pyuria, nephrogenic edema or significant proteinuria, and the earlier development of renal insufficiency, anemia and hypertension in the former. Rapoport et al.[12] and Reynolds and Edmondson[14] also commented on the mildness of the proteinuria and the absence of edema, as well as noting severe acidosis with moderate azotemia and minimal phosphate retention. Hypertension was lacking until late in the course of their cases. Papillary necrosis can be recognized on radiologic studies and should lead one to strongly urge cessation of intake of the drug.[9,15] Renal biopsy can be quite helpful in ruling out other types of renal disease.

Therapy

Treatment consists of withdrawal of the drug and vigorous antibiotic therapy of any urinary tract infection. In the belief that bacterial infection is present in all cases, whether or not there is overt evidence of it, Spühler advocates a prolonged course of antibiotic therapy, the agent being changed every month to prevent the emergence of resistant strains of bacteria.[18] The prognosis with withdrawal of the drug is good in these patients unless they are already significantly uremic[3]. Lakey's case[8] exemplifies the striking improvement in renal function which may occur.

Comments

In the face of this severe potential toxicity, one wonders if acetophenetidin is really useful enough to justify its inclusion in our armamentarium. It is interesting to note that a recent comparative study of five proprietary analgesic compounds, including the one used by the patient reported here, found no significant difference as far as rapidity of onset of analgesia, peak effect, or duration of action between plain acetylsalicylic acid and the compounds containing acetophenetidin.[21] Several authors feel that compounds containing this drug should not be advertised and should be obtainable from a druggist only by prescription.[3,5] Sweden has enacted these recommendations into law. It would seem advisable for this country to follow suit. Two of the leading manufacturers of APC compounds in this country, including the manufacturer of the offending agent in this case, have recently announced the voluntary withdrawal of acetophenetidin from their products.

Summary

Although extensively reported in the European literature, fatal poisoning from long term overingestion of Acetophenetidin has received scant attention in American journals despite significant use of the drug. It is suggested that there should be more limitation in the distribution of this drug.

Addendum

Since this paper was submitted for publication an additional case report has appeared (Plass, H. F.: Renal Papillary Necrosis Associated with Analgesic Abuse. Ann Int Med 60:111, 1964.)

I am indebted to Dr. Jorge Yunis who performed the autopsy, Dr. Richard Bruning who reviewed the sections and did the special stains, and Dr. Warren Boop who examined the brain. Dr. Richard Davis helped with photomicrography. Drs. Peter Kohler and Arthur From participated in the management of the patient and reviewed the manuscript. Drs. Maynard Jacobson, Frederick Goetz, Robert Vernier and Cecil Watson read the manuscript and offered helpful suggestions.

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12-21 will appear in the reprints or can be obtained from the author.

Ethics in Antiquity*

Among the most useful arts which contribute to sustain the faith of human nature, none can be placed above or on an equality with medicine; it ever assists the sick with material benevolence, it banishes our pains. Desist, O Practicer of the medical art, from contests that injure the patient, and if you are not able to be in accord, consult someone who can be interrogated without envy because every prudent man wants to seek counsel and he is considered the best who through frequent calls has been proved to be the wisest. In the beginning of this your art, you are consecrated by oath similarly to the priest; promise solemnly to your masters to hate iniquity and to love honesty. Remember that to sin in connection with the health of a human being is the crime of homicide. And while I honor you with the title of *comes archiatrorum* to the end that those best esteemed among the masters of the healing art shall call upon your judgment, your advice to be just arbiter in this chosen art. . . . To the expert the pulse reveals what are the internal afflictions and to his eyes the urine. Enter freely our palace, with full trust. — Theodoric the Great (454-526?)

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*Riesman, David: Medicine in the Middle Ages.

John Arderne, Proctologist — (1307-1380)

"He (the surgeon) must not be too much given to laughter or sport, and, as much as he can, he should flee the company of knaves and dishonest people, and always be occupied in things relating to his art. He should either write, or study, or pray, for the study of books is an honor to a leech. Above everything, he must always be sober, for drunkeness destroys all virtue and brings it to nought."*

So advised John Arderne, one of England's early surgeons, who termed himself a chirurgus inter medicos and who specialized in fistulas, particularly fistulae in ano.

He further urged his fellow surgeons to have clean hands and well trimmed nails, also to listen attentively but not talk too much, because loquaciousness in a doctor diminishes confidence and may even entrap him unawares. He warned his colleagues against mistaking cancer of the rectum for mere ulceration: "Explore carefully with the finger at any rate, and do not be led away and offer to operate. It will only be a disgrace to you. Warn the friends of the certain ending."**

Arderne belonged to the Guild of Military Surgeons, which had a large membership during the late Middle Ages due to the fact that England was then engaging in numerous wars. Because of their more professional training and experience the military surgeons held themselves aloof from the more plebeian barber-surgeons of the day.

When operating for fistula in ano Arderne "placed his patient in the lithotomy position. Then he first passed a probe threaded with a four-fold ligature through the fistula into the rectum, and drew out one end of the ligature through the anus and tied the two ends together. A grooved director was next passed through the fistula and a shield introduced into the rectum. After drawing the ligature tight, a scalpel was passed along the director, and with a single movement the director, scalpel, and shield were drawn out together, dividing the fistula from end to end. The bleeding was stopped by sponges wrung out in warm water, and by making the patient sit on the sponge as a pad. Afterwards he dressed the wound with dry, clean pads and a powder, held in place by a T bandage. All irritative dressings were avoided and enemata of oil given daily."***

For his pioneer work on fistula in ano Arderne can well be regarded as the first proctologist in the field of medical technology.

His fees were commensurate with his ability; for fistula surgery he charged the equivalent of $500.

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*Parker, G., M.A., M.D., M.R.C.S.: Early History of Surgery in Great Britain, p. 46.
**Ibid. p. 44.
***Ibid. p. 43

I enjoy convalescence. It is the part that makes the illness worth while.
—George Bernard Shaw

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Recent evaluations sustain these earlier judgments. In a current authoritative assessment based mainly on the factors of potency, superiority to atropine, clinical experience and physiologic study, Steinberg and Almy[2] select as the first two preferred anticholinergic drugs, methantheline [Banthīne] and propantheline [Pro-Banthīne].

The name Pro-Banthīne (propantheline bromide) sets a stamp of therapeutic authority on any anticholinergic prescription.

Side Effects and Precautions—Urinary hesitancy, xerostomia, mydriasis and, theoretically, a curare-like action may occur. The drug is contraindicated in patients with glaucoma or severe cardiac disease.

Dosage—The usual adult dosage is one tablet of 15 mg. with meals and two at bedtime; this amount may be doubled or tripled for patients with severe conditions. Pro-Banthīne (brand of propantheline bromide) is supplied as tablets of 15 mg. and, for parenteral use, as serum-type ampuls of 30 mg.

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The
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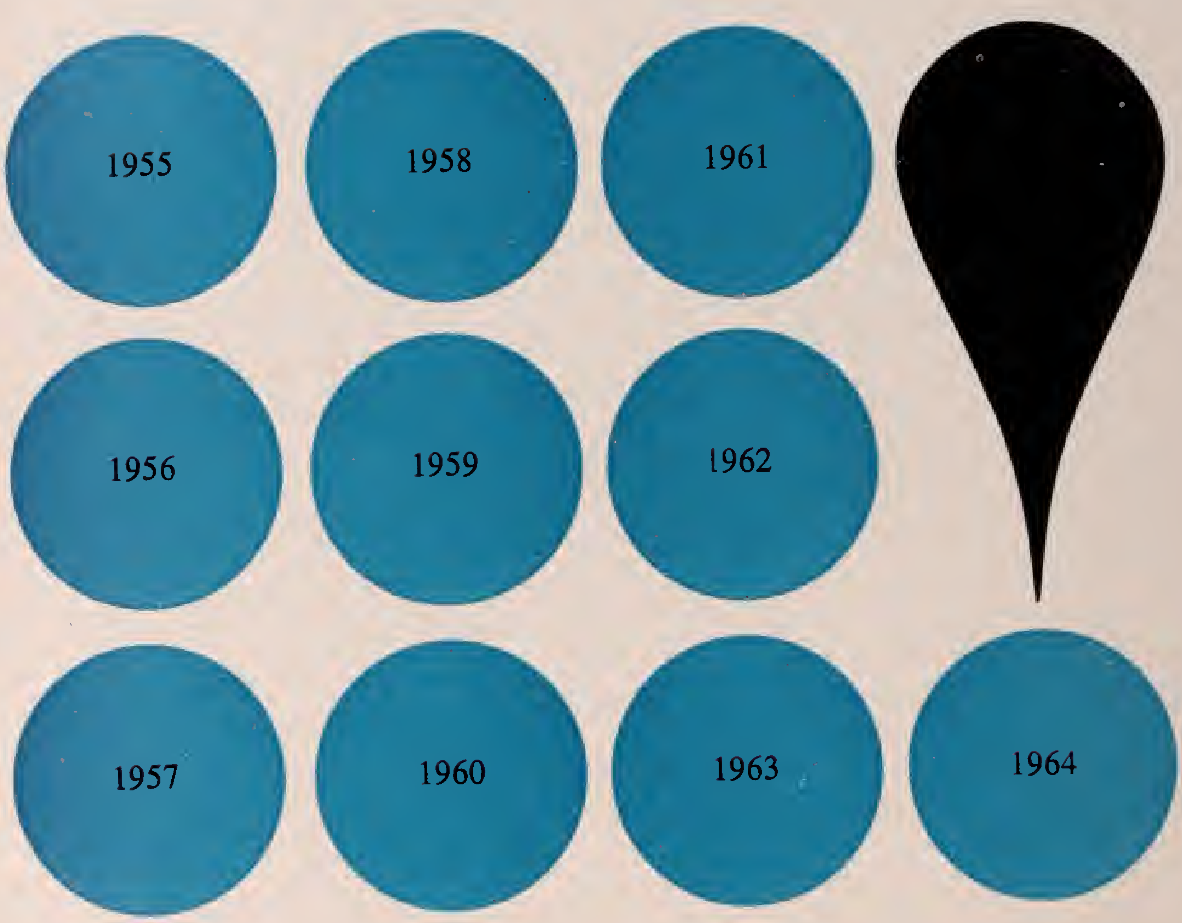
conclusion
from
10 years'
experience...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Editorials

Farewell

As I leave the Presidency of the American Medical Association I am given to many emotions. But the strongest is a deep sense of appreciation to all of you who have given me these two years, and to all who made them so memorable.

I must admit I've had the time of my life! What a delightful land we live in! What fine people are ours to know and to serve! As such we learn continually — about our profession and our country — we learn the great medical good that is daily as much a part of small towns and little hospitals as it is of the magnificent medical centers that dot the land.

There is no physician who is not important to his profession and his Association. You are the one link your patients and neighbors have with that amazing organization about which they hear so many conflicting reports. Your care for their good represents Medicine's sworn dedication. Your opinion on the many socioeconomic aspects with which we *must* be concerned makes *you* the "official" spokesman for the AMA. Your citizenship — community activity which builds as well as corrects — helps break down that myth that the doctor oversteps his boundaries when he leaves the hospital and campaigns for the best man in a general election. When you withdraw from the life around you, Medicine is out of touch.

When you vocally respect the hundreds of professions which have made our science grow so miraculously, Medicine is realistic. When you take yourself too seriously, Medicine becomes a pompous profession. When you support your local and state medical society, Medicine is united for the common good. When you fail to do so, Medicine is a house divided. But if I have given a full measure of devotion to you I am no different from thousands of our colleagues across the nation, who represent the finest in our profession by serving their patients loyally, with dedication and with good humor. If, in leaving this office, I can wish for you the great satisfaction of being a physician who is a citizen, a neighbor, an humble friend to his colleagues and his patients, then *more* I *cannot* wish you.

Edward R. Annis, M.D.
at Inaugural Ceremony
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Kidney Homotransplantation in Man: Accomplishments and Problems

THE PAST year has seen a dramatic change in the initial success rate attendant upon kidney homotransplantation in man. Twelve months ago survival following kidney homotransplantation was considered unusual whereas now it appears that around two thirds of patients receiving a kidney homotransplant are leaving the hospital with normal or adequate renal function.

These accomplishments have not been achieved in one giant step but represent the happy synthesis of contributions made by so many investigators that it would be unfair to name only those who have participated in the most recent advance. The ingredients of success as far as the present situation is concerned, however, can be identified. First of all is the recognition that impending rejection of a kidney homograft can be reversed by certain measures; specifically, the administration of steroids in large doses, the injection of the cytotoxic drug Actinomycin C, and local irradiation of the kidney either singly or more usually in various combinations. These measures are ordinarily employed vigorously for relatively brief periods of time, followed by reduction and in most instances elimination of the agent as renal function recovers to normal. Second has been recognition that sepsis which is perhaps the most common cause for early failure can best be controlled by manipulating drug dosage in such a way as to maintain the leukocyte count in the normal range. In particular the drug Imuran which serves as the basic drug for suppression of the immune response can produce profound leukopenia if dosage is maintained too high for too long. In spite of high dosage with Imuran most patients will proceed to mount a rejection reaction against the transplanted kidney, necessitating the use of supplemental measures as mentioned earlier. If leukopenia is present at this time, the stage is set for septicemia. Third has been recognition of the importance of transplantation of a healthy kidney from a blood relative. Homotransplantation of a healthy kidney from a living donor usually means that a functioning kidney is obtained which permits early recognition of the appearance of a threatened rejection allowing the application of measures to reverse rejection at just the right time. Added to this are the benefits derived from the early rapid restoration of renal function in terms of nutrition. The use of a blood relative as the donor appears to be of real importance in increasing the likelihood of acceptance of the homograft. This is undoubtedly due to the increased likelihood of donor and recipient sharing similar genetic determinants of antigens which are involved in the homograft reaction. The validity of this viewpoint is supported by extensive experimental data particularly in mice, in which all gradations of genetically determined antigenic differences are recognized which correlate well with the degree of difficulty encountered in accomplishing successful homotransplantation of tissue.

Although the picture of initial success in kidney homotransplantation is bright in comparison to the recent past, it is obvious that this is really only a beginning. An early mortality of 40 per cent offers a challenge for improved methods. Late failures are already recognized. The observed occurrence of repeated rejection attempts and the finding of histologic evidence of continuing reaction of host against transplant suggest that late failures will increase with the passage of time. Thus it is obvious that many challenges remain.

In line with the observations that close genetic relationships favor the successful induction of homograft tolerance, many investigators are seeking means of identifying or recognizing major differences (termed histocompatibility differences) in the antigenic makeup of individuals. Perhaps the most promising techniques involve the iden-

Continued

In systole and diastole, the human heart produces a maximum signal of only a few millivolts between two ECG limb electrodes. Mixed in with this tiny signal may be some unwanted electrical "noise", caused by power lines, nearby X-ray or diathermy machines, or even ordinary office equipment. Until now, eliminating this noise from the record usually meant time-consuming adjustments and rerunning records until the complexes were clear.

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tification of reactions between prospective host and donor which occur when lymphocytes obtained from the prospective recipient are injected intradermally in the prospective kidney donor. A skin reaction similar in appearance to the Mantoux reaction occurs which seems to correlate with the intensity of rejection of tissues subsequently grafted from donor to recipient. Thus, it might be possible to choose as a donor the individual whose tissue antigens provoke the least reaction by the lymphocytes of the prospective recipient. Refined in vitro techniques employing tissue culture of recipient lymphocytes with donor antigen hold out the prospect of more quantitative measurements. Other investigators are trying to identify leukocyte antigens and correlate these with the homograft reaction.

The search continues for a safer and more effective drug which will suppress the immune response to the foreign tissue. An agent or technique which would eliminate the need for administration of massive doses of steroids would do much to improve early mortality which is frequently related to infection and impaired healing and occasionally to gastrointestinal bleeding which are complications of the use of these agents.

An alternative approach to the problem of improving the safety and effectiveness of drug-induced homograft tolerance which has as yet seen little application is the technique of antigen loading. Various members of our own group at the University of Minnesota including Martinez, Good, Kelly and Aust have been carrying out studies of tolerance induction in animals by a variety of techniques employing antigenic material obtained from the donor as the conditioning agent without using immunosuppressive drugs. Our observations along with the findings of other investigators support the general concept that the quantitative relationship between the antigen on one hand and the lymphoreticular cell mass of the recipient on the other hand are of great importance in respect to development of either immunity or tolerance. Tolerance may be regarded as an immune response in which the tolerant animal is specifically incapable of responding to a given antigen although he retains a normal ability to respond to other antigens. The aforementioned investigations have stressed that under conditions in which the amount of antigen presented to the host is very large in comparison to the amount of lymphoreticular cell mass available to respond to the antigen, the condition termed tolerance is most likely to occur. Present techniques employed clinically depend on the use of the immuno-suppressive drugs to limit the ability of the lymphoreticular tissues to respond to the antigen as well as to reduce the mass of the lymphoid tissues. These measures, in particular the use of steroids, subject the patient to an increased risk of sepsis, impaired wound healing and gastrointestinal bleeding. As an alternative antigen loading in which the amount of antigenic material presented to the kidney recipient from the kidney donor is increased with the expectation that a smaller amount of immuno-suppressive drug therapy would be required appears promising. Perhaps even more important would be the possibility of producing a more complete state of tolerance compared to the partial tolerance achieved by the current techniques.

Another important problem is that of precise identification of a threatened rejection reaction. Occasionally, rejection of the transplanted kidney begins within a matter of hours after transplantation. This can pose a real problem in distinguishing threatened homograft rejection from acute tubular necrosis secondary to ischemia. To explain these early rejections in terms of a homograft reaction, it is necessary to postulate presensitization of the recipient by means of previous blood transfusions which result in sensitization to minor blood group antigens or to antigens present in the blood donor leukocytes which may be shared with the donor kidney. At the other end of the scale, the onset of a rejection reaction may be more subtle than is usually the case. It may extend over a relatively long period of time, eventually leading to the same disastrous consequences as the more vigorous early rejection. The problem of identification of threatened re-

Continued

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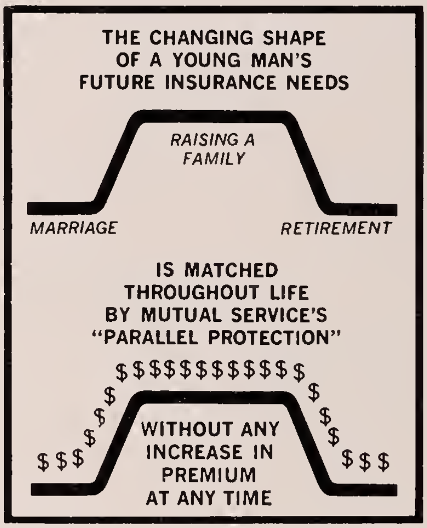
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City__________________State________Zip______ jection is being attacked by a variety of techniques. In some instances the appearance of a threatened rejection reaction may be identified by the observation of tubular epithelium in the urine or by the appearance of large numbers of lymphocytes in the urine. The technique of kidney biopsy and identification of antigen-antibody reactions by the use of fluorescent staining techniques is another promising approach to the recognition of specific immune rejection of the kidney. Changes in serum enzyme level such as lactic dehydrogenase also under study may prove to be of value in indicating the onset of the threatened rejection reaction.

There is a continuing real interest in the possibility of using organs obtained from individuals who have died under suitable circumstances, such that one could anticipate the possibility of function in the transplanted kidney. In certain instances a suitable living blood relative is not available to serve as a donor of a kidney. In addition where attempts are being made to extend transplantation to other organs such as the liver and heart, a source other than a living human donor must be sought. Although there have been successful cases involving the use of fresh cadaver kidneys, the damage sustained by the kidney during the process of dying and the increased length of time normally associated with the transplantation of an organ under these conditions both result in the frequent occurrence of serious impairment of function. The combination of a damaged kidney plus the additional damage which results during the adaptation period when the host is attempting to reject the kidney may result in a significant degree of permanent damage even if the kidney should be accepted. More serious is the fact that the present technique of drug therapy depends upon recognition of the threatened rejection and treatment with massive doses of steroids at a critical time. Since the transplanted cadaver organ frequently is not functioning well at this time, there is no way of recognizing the threatened rejection which then can proceed to completion. Although considerable effort is now being made to preserve organs for varying periods of time, this may not substantially improve the results obtained with cadaver organs since these organs have been injured prior to death in most instances. As a partial solution to this problem techniques are being developed which will permit one to evaluate the function of a kidney obtained from a cadaver before surgically implanting it. A more ambitious extension of this technique might permit actual resuscitation of seriously injured though viable organs.

Meanwhile, other investigators have turned to the use of heterografts as a solution to the problem of organ source. Although a surprising degree of temporary success has been achieved with these organs, it seems unlikely in the light of past laboratory experience that heterografts will prove to be satisfactory, employing the current technique for the induction of tolerance. This is based on the fact that the reaction of a recipient to a heterograft is invariably much stronger than it is to a homograft. Nevertheless, with improvement in the techniques employed in the induction of tolerance, the use of heterografts in certain situations may ultimately be feasible.

William D. Kelly, M.D.
University of Minnesota

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*Professor, Dept. of Surgery, University of Minnesota.

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Iliofemoral Thrombophlebitis*

THE ETIOLOGY of deep venous thrombosis is obscure. Stasis, injury to the intima, and blood dyscrasias are causative agents. With the use of anticoagulant drugs there has been a great reduction in the number of deaths from pulmonary embolism and in the incidence of subsequent venous insufficiency from iliofemoral thrombophlebitis. The severity of the postphlebitic syndrome is proportional to the extent of the original thrombophlebitis and to the adequacy of treatment.

The diagnosis of deep thrombophlebitis of the calf veins may be difficult. Pain is the most constant early symptom and should be the warning sign. Treatment consists of anticoagulants, hot packs, elevation, and external supports.

The diagnosis of an iliofemoral thrombophlebitis is not difficult. The limb is usually edematous from the inguinal region to the toes and there is tenderness in the femoral triangle. The thrombosed femoral vein may be palpable. Anticoagulant therapy should be continued until the patient is completely ambulatory and without pain.

Adequate support in the form of a well fitted surgical stocking is essential. The support should be worn continuously for at least six months, then gradually discontinued.

In 1957 Mahorner introduced femoral thrombectomy, a surgical procedure that attempted to restore the function of a thrombosed vein and prevent the occurrence of the postphlebitic syndrome.

Phlegmasia Cerula Dolens is an iliofemoral thrombophlebitis with total or near total venous occlusion of the limb resulting in obstruction to the outflow of blood. It is characterized by sudden onset, massive edema, violaceous discoloration of the skin, and ecchymosis. Arterial pulsation may be reduced or absent. The edema and ability of muscular movement help distinguish the disease from an acute arterial occlusion. It is rare and may be associated with metastatic carcinoma. It may cause gangrene of a digit, occasionally gangrene of an extremity, and even death. Treatment is directed at stopping the progression of the clot, decreasing the edema and relieving the pain. Femoral thrombectomy is advisable in this type of thrombophlebitis, offering a greater assurance than does conservative therapy, which is preferred in uncomplicated iliofemoral thrombophlebitis.

Clarence V. Kusz, M.D.
Minneapolis, Minnesota

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*See Iliofemoral Venous Thrombosis, Harrison Farley, M.D. et al. Minnesota Med 47:5:507, 1964.

The Editor's Soliloquy

Etiology: Attaching the Blame

With a few aches and pains here and there, some people dream up an old accident of a few years back in search of someone to blame and sue.

In the physiologic process of growing older,* and in the suboptimal physical condition in which many people maintain themselves, it is common that these individuals may be aware of a variety of aches and pains that have no other clinical significance. To attribute these physiologic changes to an incident, or to endeavor to establish an etiologic factor which removes the blame from one's self, merely delays the relief which might otherwise be attained.

It should be the responsibility of physicians to explain to their patients these physiologic processes, rather than to be eternally searching for a scapegoat.

Is it possible that the ever increasing incidence of psychosomatic disease is iatrogenically induced?

Carl O. Rice, M.D.

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*Overweight, lack of physical trim, morning stiffness, minor excesses and dissipations.

Photographic Contest

The Editors of MINNESOTA MEDICINE, in collaboration with the Doctors' Photographic Society of Minneapolis, take pleasure in announcing a monthly photographic contest. The contest is to promote an interest in photography in the medical profession. First prize each month will be publication in full color of the winning picture in MINNESOTA MEDICINE.

The following rules will govern the conduct of the contest:

1. Only doctors of medicine are eligible to submit pictures, and the picture must have been taken or composed by a physician.
2. Each contestant may submit not more than two pictures each month.
3. Only color transparencies, 35 mm. to 2¼" can be considered.
4. Each slide should be labeled with the marker's name, address, and the identifying title.
5. Slides should not be mounted in glass, but can be protected in plastic sleeves or envelopes.
6. Each entry must be accompanied by a self-addressed, stamped envelope if return of the picture is desired. Returns will be made shortly after the close of the contest each month. The winning photograph will be retained but will be returned after it has been used.
7. The deadline date for entry will be the 10th of each month and the winner of each month's contest will be announced in MINNESOTA MEDICINE in the subsequent issue. The date of publication will be three to six months in advance.
8. There will be no limitation on subject material except as indicated in item 10.
9. Model releases will be requested of winners where appropriate.
10. Judges will be selected by the editors of MINNESOTA MEDICINE and the Doctors' Photographic Society. The judges will be guided by the precepts of the Photographic Society of America, and winners will be based on appropriateness, interest, impact, and technical excellence.
11. The editors of MINNESOTA MEDICINE and the Doctors' Photographic Society cannot be responsible for entries lost or damaged, but every effort will be made to protect submitted pictures.
12. The first judging was made in the month of February and has been monthly thereafter.

Your pictures are hereby invited. Please submit pictures to:

Photo Contest Editor
MINNESOTA MEDICINE

Curbstone Consultation

Treatment of Fractures

QUESTION: What is the relative importance of alignment versus apposition in the treatment of fractures of the long bones in children?

M.D., Minneapolis

ANSWER: Side to side femur, and humerus, and to a lesser degree the bones of the forearm and tibia, as contrasted with end to end apposition. This also allows for the temporary stimulation of growth in the affected bone.

A certain amount of angulation is compatible with a good result in long bone fractures in children, particularly if the angulation is close to one of the ends or epiphyses. In such instances, the bone will remodel in line with the function of the adjacent joint and the end result will be complete obliteration of the initial angulation and a perfectly functioning extremity. All of these points are emphasized to eliminate the use of open reduction or internal fixation, with a few notable exceptions in children as compared to adults.

These principles are not new but re-emphasize the precepts known to all experienced orthopedic surgeons and emphasized in the text on Fractures in Children, by Walter P. Blount, of Milwaukee.

Robert P. Keiser, M.D.
Coral Gables, Florida

Langer's Arch

QUESTION: What is Langer's arch and is it of any clinical significance?

M.D., Rochester

ANSWER: Langer's arch results from an anomalous muscle which traverses the axillary cavity extending from the lateral border of the latissimus dorsi to the undersurface of the insertion of the pectoralis major. It probably occurs in about five per cent of individuals, but in only a relatively small percentage is it developed to an extent to be of clinical importance. The chief clinical significance of this structure is that when presenting as a mass in the axilla, this anatomic variation must be differentiated from pathologic conditions in that region. This structure may lead to confusion in such operations as radical mastectomy if the surgeon is unaware of its existence.

If children grew up according to early indications, we should have nothing but geniuses.—Goethe

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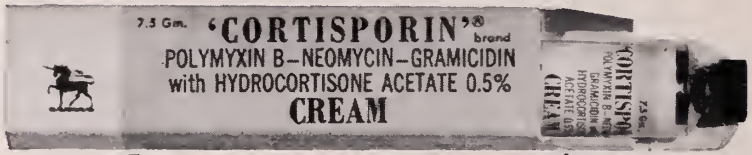

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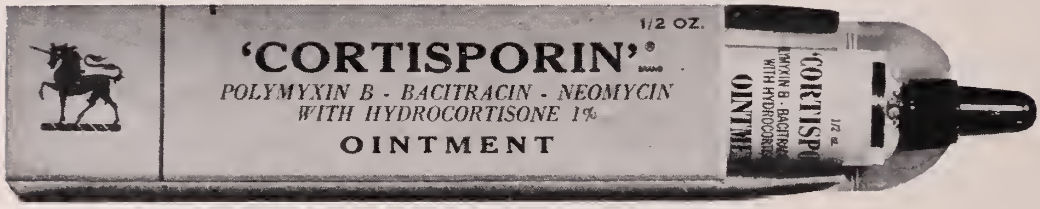

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Fracture–Trauma Conference

Occlusion of the Internal Carotid Artery Secondary to Closed Cervical Trauma

Relatively few cases have been reported of internal carotid artery occlusion subsequent to nonpenetrating cervical trauma.[1-5] Of the seventeen cases reported, nine survived but all had residual neurological deficit. Associated bony injury to the skull, mandible, or vertebrae was often present.

The signs and symptoms are usually evident immediately after the injury. The deficits may vary from complete paralysis to more protean defects, depending upon the site of injury, the propagation of the clot within the carotid vessel, or the embolization that might occur to different radicals of the vascular distribution in the brain. The onset of signs and symptoms may be delayed for as long as 24-30 hours.

Although the exact mechanism of injury is uncertain, the most probable explanation is direct blunt force suddenly compressing the artery against the surrounding bony structures with resultant intimal injury. Spasm, thrombus formation, edema, and reduced flow probably act in a vicious circle to promote eventual occlusion. Complete disruption of the intimal and/or media undoubtably occurs (as in closed thoracic aorta injury) in the more severe trauma. However, as only two patients have had direct exploration,[5] the exact pathology remains in doubt.

As reported in the literature, treatment has consisted of anticoagulants, cervical sympathetic block, superior cervical sympathetic block, and recently carotid artery exploration and removal of thrombus.

The following case report is of a patient who suffered a closed injury to the right carotid artery.

Continued

Case Report

A 27-year-old white female was injured in a two-automobile collision on 6-4-62. The details of the accident were unknown. The patient was comatose following the accident. A left hemiplegia was noted shortly afterward. The patient required tracheostomy, gavage feedings, and urinary catheter drainage.

She was transferred to Methodist Hospital on 6-18-62. At this time she was examined and the pertinent findings demonstrated a normotensive, semi-stuporous white female who had left hemiparesis with increased deep tendon reflexes of the left extremities. Positive bilateral Babinski reflexes were observed. The pupils were equal. There were old ecchymoses and healing abrasions of the right cervical area. The tracheostomy was functional.

The laboratory data and multiple X rays are not pertinent. No fractures were found in the skull, neck or chest.

On the following day, bilateral cerebral angiography was performed. The left carotid system intra-and extra-cranially was "normal." However, there was only minimal filling of the right extracranial internal carotid artery (Fig. 1).

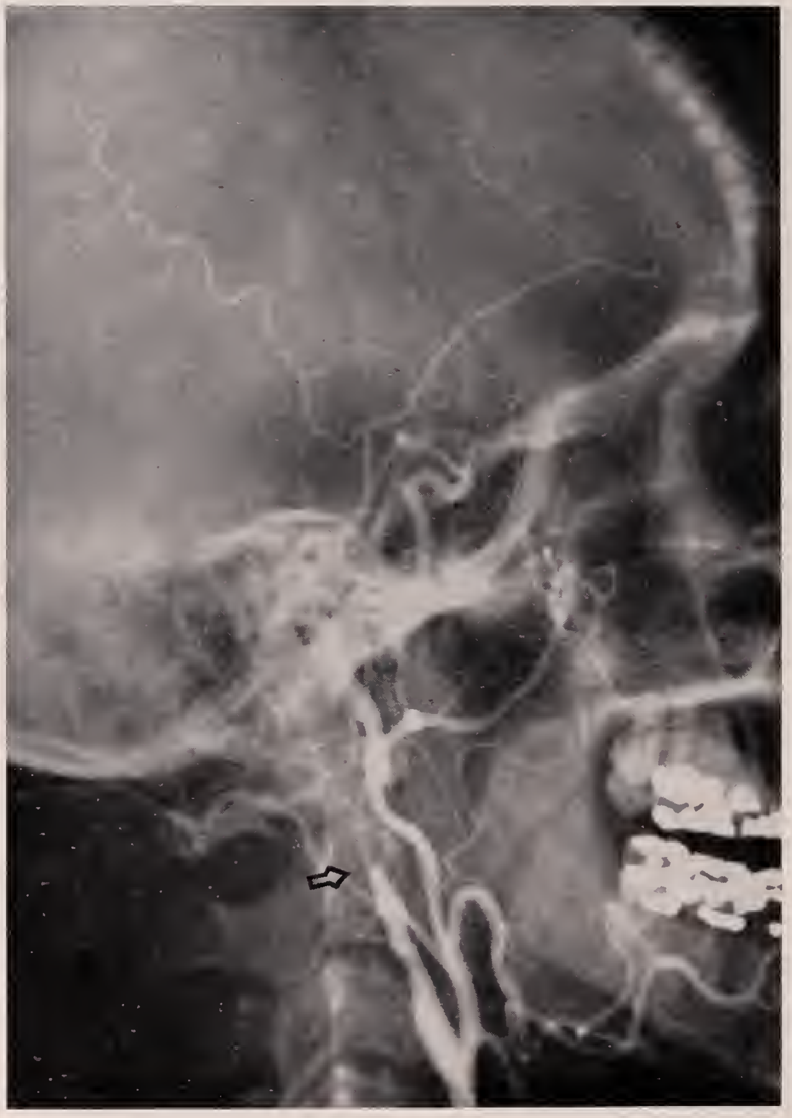

Fig. 1 — Percutaneous right carotid artery angiogram demonstrates the normal external carotid artery and the obstructed internal carotid artery (arrow). Partial filling of the internal carotid artery and syphon distribution distal to the obstruction result most likely from collateral anastomotic arteries.

Subsequent exploration of the right carotid artery demonstrated massive scarring in the cervical tissues, with complete and permanent obstruction of the internal carotid at the base of the skull as revealed by direct carotid angiogram done at the time of surgery.

Postoperatively the patient gradually improved, but subsequent evaluation showed residuals of permanent mental and peripheral central nervous system deficit.

Discussion

Initial examination at the time of injury indicated that the patient had sustained direct cervical trauma (ecchymoses, hematoma, abrasions) in the area of the right common carotid artery. The subsequent course and angiographic findings suggest that an internal injury with thrombus resulted, and then embolization of the thrombus occurred into the right internal carotid system.

Although not always possible, because of other contraindications, the performance of immediate carotid angiography in such patients with traumatic hemiplegia might demonstrate salvageable vascular problems.

Summary

Traumatic carotid artery injury and neurological deficits may result from nonpenetrating injuries of the neck. Immediate carotid angiography should be performed (if not otherwise contraindicated) if patients are to be salvaged without neurological residual.

Jerome T. Grismer, M.D.
Paul S. Blake, M.D.
Minneapolis, Minnesota

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In this atomic age, man is the one upon whom the peace of creation depends. — We sow the seed of suffering as well as freedom. — The healing hands of the physician are the healing hands of God.

—The Very Reverend C. Julian Bartlett, D.D.
Grace Cathedral, San Francisco,
June AMA meeting.

There are three kinds of brains: one understands of itself, another can be taught to understand, and the third can neither understand of itself nor be taught to understand.—Niccolo Machiavelli

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Tumor Conference

Excision of Metastatic Pulmonary Nodule

Pulmonary nodules due to metastatic malignancy present the physician with a perplexing therapeutic decision. The feasibility of resection of malignancy metastatic to lungs is receiving increasing attention in recent medical literature. Formerly in the follow-up examinations of patients with cancer the finding of a nodule on the chest X ray was interpreted as a hopeless prognosis and was approached with an attitude of despair. Survival rates after removal of metastatic chest nodules equal the survival rates after surgical therapy of primary bronchogenic carcinoma.

Case Presentation

Patient A. C.: This lady was 64 years old when she first entered Hennepin County General Hospital on January 12, 1955. At this time she had complaints of crampy abdominal pain and vomiting. On January 14, 1955, she underwent a transverse colostomy for colonic obstruction. A subsequent barium enema revealed a constricting lesion of the sigmoid colon. On January 27, 1955, she underwent subtotal colectomy for adenocarcinoma of the colon with lymph node metastases.

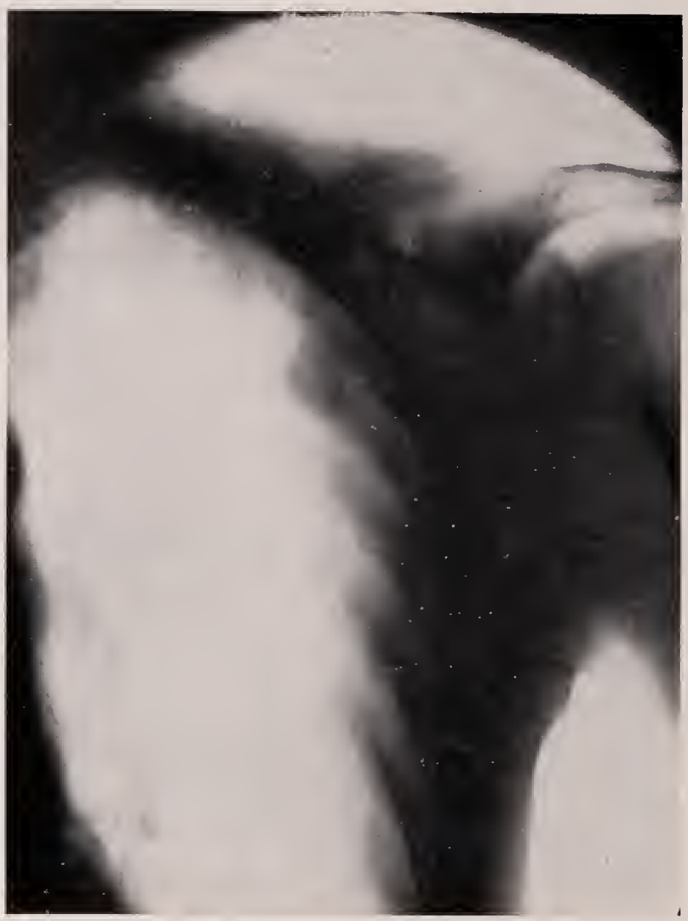
In the Outpatient Department she returned faithfully for follow-up checks and remained well. In July, 1958, three and one-half years following her colectomy, a nodule appeared on her chest X ray. (See Planogram on next page.) The patient remained asymptomatic. There was no evidence of other metastases. On August 14, 1958, a laparotomy was performed which revealed no evidence of residual cancer within the abdomen. On the same day a thoracotomy and wedge resection of the nodule in the left upper lobe was performed. Sections of the nodule revealed mucus-producing adenocarcinoma, which were compared with slides from her colonic malignancy and found to be very similar. In the opinion of the pathologist the pulmonary nodule was a metastasis from the colon tumor.

Once again the patient faithfully returned for follow-up examinations. She has remained asymptomatic and without evidence of recurrence of the disease. She was examined most recently on March 12, 1964, five years and nine months after the pulmonary resection and nine years and three months after her original colonic resection.

Conclusions

Removal of solitary metastatic pulmonary nodules is occasionally rewarding. This is particularly true if the primary malignancy was of colon or renal origin.[1] A longer latent period between the initial resection of the

Continued



malignancy and the appearance of a pulmonary metastasis renders the prognosis for cure more favorable.[1] Indications for resection of metastatic pulmonary nodules are:

1. Control of primary malignancy.
2. Absence of other metastatic disease.
3. Accessibility for resection.[2]

It should be borne in mind that a previous malignancy does not negate the possibility of a new primary lung tumor. In a large series of resected metastatic pulmonary nodules the five-year survival has varied from 14 to 30 per cent.[3-5]

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Hennepin County General Hospital
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He must have had a magnificent build before his stomach went in for a career of its own.—Margaret Halsey

Clinical Path Conference

Sudden Death*

Anthony Voytovich**

I would like to read the protocol for the case we are presenting today. Members of the audience can follow along on the copies they have in their possession.

Protocol

Chief Complaints

This is the first admission of this 64-year-old negro lady, following two weeks of vomiting two to three times a day.

Present Illness

One year prior to admission the patient had had a severe cold from which she hadn't fully recovered, with nonproductive cough and malaise continuing thereafter. Three months prior to admission there was a marked behavioral change (with increasing lethargy and irrational speech), which became increasingly severe. One month prior to admission she had stumbled and fallen; shortly thereafter she became inactive and unresponsive, and remained so. Two weeks prior to admission she began vomiting two to three times a day.

Past History

Known abdominal mass two and a half years. No serious illnesses or hospitalizations. No contact with syphilis or TBC. No clinical record.

Physical Examination

BP 160/100; P 98; Resp. 30; Temp. 103. Gen: Extremely obese, semicomatose lady with nonproductive cough. Skin dry. Eyes, ears. nose and throat: Bilateral cataracts; pupillary reflexes sluggish; tongue dry. *Neck:* No adenopathy or rigidity. *Chest:* Coarse, scattered, changing rales throughout both lung fields. *Heart:* Regular rhythm, sounds diminished, no murmurs or rubs. *Abdomen:* Distended, with strong, hard, nontender, smooth, movable mass 10 x 20 cm. in right lower quadrant extending to midline. Bowel sounds active. *Rectum:* No masses. *Pelvis:* Cervical discharge. *Extremities:* No edema, varicosities or clubbing; extreme weakness, with occasional fasciculation. *Back:* Diffuse costovertebral angle tenderness. *Nerves:* Deep tendon reflexes symmetrically increased. No Babinski or localizing signs.

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*Presented on 1/29/64 at State University of New York, Upstate Medical Center, Syracuse, N. Y.
**Senior Medical Student.

Laboratory Admission

Urine SG 1010, ph 5.5, cloudy, 4+ alb., sugar neg., 20-30 WBC HPF in clumps, 1-2 gran. casts, many bact.; HCT 44 Hgb 14.5, WBC 8600, 66 segs., 4 bands, 23 lymphs, 7 monos; BUN 12; spinal fluid opening 220 mm., closing 170 mm., cloudy yellow, 579 segs., 177 lymphs, chloride 107, sugar 80, protein 136.

Fourth Day:

Spinal fluid 383 WBC polys, prot. 169, cl 107, sugar 50, smear, culture india ink mount not remarkable, all blood cultures neg., bilirubin .5, transaminase 22; CBC now WBC 13.8, 60 polys, 8 bands, 30 lymphs, 2 monos.

X Rays

Chest: Fine miliary densities both lung fields. No evidence effusion, atelectasis or segmental consolidation.

Abdomen: No hepatosplenomegaly. Right kidney poorly visualized; 10 x 20 cm. soft tissue mass with curvilinear calcium at outer margins suggesting cystic component. Mass elevates transverse colon.

Skull: Negative.

Hospital Course

Given IV fluids and ½ gram chloromycetin bid for three days. Became afebrile second day but fever returned third day along with transient nuchal rigidity. After above laboratory work, patient was transferred to City Hospital and begun on para-aminosalicylic acid, Isoniazid, Pyridoxine, Streptomycin and acetylsalycylic acid. On fourth day condition worsened with increasing respiratory distress, so oxygen tent and aqueous penicillin were begun. On fifth to ninth day the general condition so improved that all medications were discontinued and TBC discarded. Patient became afebrile, increasingly active, strong and responsive, and ambulation was begun. On ninth day patient sat up in bed, suddenly became apneic, and failed to respond to usual resuscitation methods.

Now Dr. Head will describe the X-ray findings and then Dr. Bunn will discuss the case. Dr. Rohner will conclude by presenting the pathology found from the autopsy examination.

Dr. Joseph A. Head*

The characteristic of the chest film is that there are tiny nodules throughout, producing a rather diffuse pattern, equally localized everywhere. There are no areas of consolidation and none of atelectasis. There is also no evidence of pleural disease so far as I can tell. She does have a large left ventricle and her aorta is a little more prominent than normal, but certainly not remarkable for a patient this age, with a slightly elevated blood pressure. She does show definite left ventricular hypertrophy.

In the abdomen, in the region of the right kidney, she has a large somewhat lobulated mass with calcification, resembling degenerated neoplasm. However, owing to the size of this mass and the fact that it has been present for two and one-half years, I would be more inclined to interpret it as a large, lobulated cystic mass of the right kidney, with calcification in its margins. The remainder of the abdomen and what I could see of the dorsal spine and pelvis were normal.

Radiographically these nodular densities have all the characteristics of miliary tuberculosis. One can have similar nodular densities throughout the lungs owing to such entities as hemosiderosis or a diffuse idiopathic type of fibrotic change, but usually in other diseases of that kind there is less homogeneity of the nodular pattern. Despite the progression of events elaborated in the protocol, I think we still have to consider the diagnosis to be miliary tuberculosis until proven otherwise.

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*Assistant Professor of Radiology, State University of New York.

Dr. Paul A. Bunn*

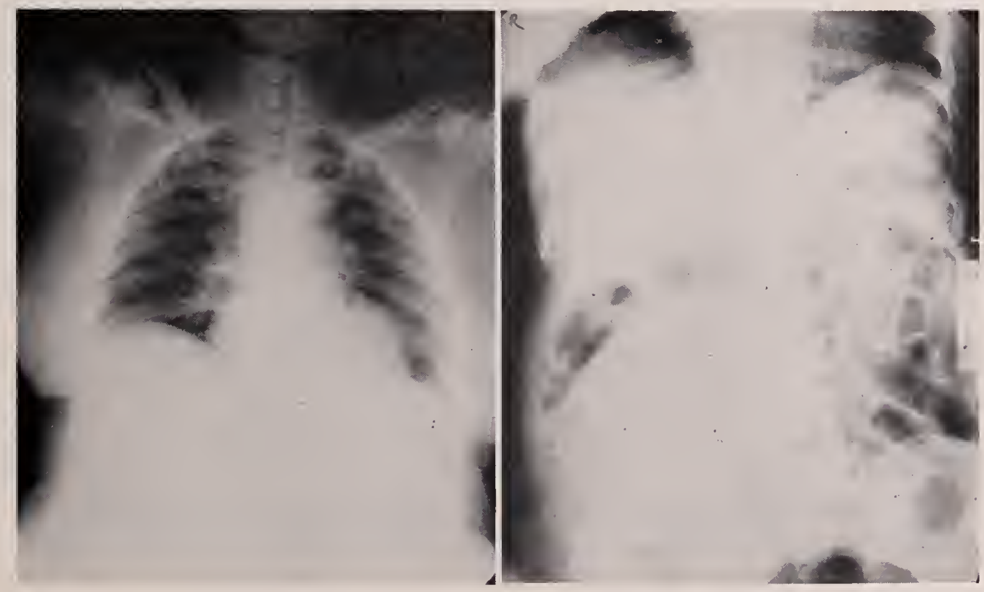
It is perfectly evident that this patient had meningitis of chronic variety, for which the two most common causes are tuberculosis and syphilis. The diagnosis of syphilis is not possible here because we do not have the serological test, and in the past medical history no contact with syphilis was mentioned.

Meningitis

This patient had meningitis; all the symptoms fit that picture: she had fever, she vomited, she was confused, she showed personality changes, she suffered weakness, she finally fell down, she had abnormal spinal fluid, and she died — because of inadequate treatment. Furthermore she was a Negro — in the proper age group, the sixties, for tuberculous meningitis and miliary tuberculosis. For over a year she had had the respiratory disease from which she failed to recover, and she had had the central nervous system symptoms for nearly three months. Furthermore, the miliary lesions which Dr. Head has so well described are classical of tuberculosis. She had the proper cell count and distribution of cellular and protein elements in the spinal fluid, and she had no anemia. All of these findings fit tuberculosis. On the other hand, is is certainly true that in older age groups tuberculosis generally follows some primary focus, which in the Negro is often the skeletal system. We have no information available either from the X rays or from the story that in this case the patient had any bone disease.

Tuberculosis

The one area which we could conceivably focus on is the large mass in the abdomen. I presume this could be tuberculous — although the mass is much too big for any description of a tuberculoma in the body that I have ever read about or seen.



Chest X ray   Flat Plate of the Abdomen

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*Professor of Medicine, State University of New York.

Continued

There are certain facts inconsistent with the total picture. First, the patient did not die correctly. She sat up in bed, became apneic, and expired rather suddenly. This does not conform to tuberculous meningitis. Neither does the remission that preceded death, occurring between the fifth and the ninth day. Furthermore, a description of the bacteriological results was omitted, and I presume that there were no tubercle bacilli isolated from either urine or spinal fluid, or, for that matter, from the sputum, because none are recorded. It would have been most convenient for this discussion, had they been recorded. The point is then: her death was irregular, since the mass was too big for a tuberculoma.

By way of three "M's" for this patient, we have to explain the mass, the miliary lesions, and the mode of exodus. I will, for the moment, presume that she had tuberculosis. Except for the mode of exodus, the whole story is classical for tuberculous meningitis. I would like to give you a few facts about tuberculous meningitis that perhaps are not well known or described in textbooks of medicine or pathology. It is a disease which persists for anywhere between one week and three months; 32 weeks is the longest I could find in the literature. The temperature that this woman presumably had was at least 103°F; subsequently the fever ran a course as described for tuberculosis or tuberculous meningitis. Such a temperature pattern is irregular and unpredictable. The temperature itself is usually hectic, often typhoidal, and unpredictably remittent with the first few days of treatment. Furthermore, it is often observed that the patient's temperature will in fact reach a crisis; it will remain low for only a few days, later to relapse.

No Weight Loss

The woman is described as being extremely obese, which is consistent with tuberculosis. She apparently was not a very hard worker. She was a good eater, and even though she may very well have had pulmonary tuberculosis or some other focus, it did not trouble her, and she remained fat. A loss of weight in tuberculosis occurs only with rapidly active disease and in the instance of meningitis only at the end when the fever becomes very high.

Eye Grounds

In miliary tuberculosis with tuberculous meningitis the presence of miliary lesions in eyegrounds would be more diagnostic, but unfortunately, cataracts in this woman prevented the lesions from being seen. Some of you in the last few months have had the opportunity to see a miliary tubercule in the eyeground, which, once seen, is so classical that no organisms in the laboratory are required to prove the diagnosis.

Clinically Normal Spleen & Liver

Furthermore, this woman, despite her various bodily ailments, had no enlarged spleen or liver. This is interesting in tuberculosis of the miliary variety or meningitis because the spleen and liver are generally not enlarged, even though at autopsy they are loaded with mycrobacteria filtered by the spleen and other reticuloendothelial systems.

Spinal Fluid

One of the observations which has to be made and which is now more or less misleading concerns the constituents of spinal fluid in patients with tuberculous meningitis; chlorides and sugars will be unduly lowered. In the early weeks of the disease chlorides vary widely and in about two thirds of the cases may actually be normal. Similarly, the sugar concentrations vary widely, with a direct proportionate number between white cells and the sugar content. With a cell count of 350 or 400, one would not anticipate that the sugar content would necessarily be low, although in this individual it was slightly decreased. The variations observed here between the two lumbar punctures — the spinal fluid protein content took an appreciable dip as did the sugar — is not at all surprising, for these changes will be observed day by day. One of the explanations for the rapid change in protein in spinal fluid disease with tubercule bacilli is the fact that the products of inflammation are frequently released unpredictably and in great concentrations; when that happens, the concentration of protein obviously will vary tremendously, so that day to day changes from 136 to 169 or even 220 are not unusual. Similarly, the cell counts may vary tremendously from week to week, that is, the distribution of the poly count, the total count, and the number of lymphocytes. Early in the course, almost uniformly, there will be "polys." Only late in the course, prior to death, will there be a predominance of the lymphocytes. These observations are all in favor of this patient's having tuberculous meningitis.

A Focus for Tuberculosis

The one "hooker" is that almost universally at the age of sixty there has to be a focus of tuberculosis outside the central nervous system to account for the dissemination. As suggested earlier, in the majority of patients, in particular the negro female, the skeletal system provides that focus. Now we are talking about series of patients and not single individuals; but it is variously estimated that in some groups as many as 75% of the cases of miliary and meningeal tuberculosis in the adult female Negro follow skeletal disease. These series obviously are composed of small groups, but nevertheless, this is an observation recorded over and over again.

The second most common focus is the kidney. The third is the lung, exclusive of small residual scars or perhaps an inactive or healed secondary kind of tuberculosis in the lung. I am talking here about an open active focus as the seeding source for distribution of the "bug" into the blood and into the central nervous system; but in the female Negro, aged 60, the lung is the third most common focus. There is no large or cavitary pulmonary lesion visible radiographically, and it would be surprising to expect a small pulmonary lesion to cause a huge dissemination. The type foci which cause dissemination generally are open and active. There is in this series of X rays, however, no evidence of skeletal disease; but there is present the second most common focus — major kidney disease. In tuberculosis it is a rather important phenomenon that if the large mass is associated with the kidney, it probably would indicate tuberculosis arising from the kidneys. It is always true, moreover, that when one sees disease to this extent in one of two bilateral organs, the other has to be involved. Renal tuberculosis of the advanced stage, acting as the focus for the subsequent meningitis, is uniformally bilateral, producing organisms from both sides.

Continued

The Cause of Sudden Death

In individuals with tuberculous meningitis death may supervene from cerebral arteritis with brain destruction. These patients develop internal hydrocephalus from blocking of the spinal fluid circulation, with uncommon rises of the central nervous system pressure and resultant brain damage. They can die from general debility due to toxicity from the disease, or from miliary tuberculous seeding, interfering with the function of a number of different organs. These patients gradually deteriorate and die, in a matter of weeks — not abruptly in one day. One might consider that the five-day remission in this case was just a lull before the storm. It is not unusual for the patient who first gets isoniazid to become afebrile rather promptly; but to have her become strong, responsive, and ambulating is a little too much to be consistent with tuberculous meningitis. The patient may have intermittent periods of getting better and worse, but never wholly well. *In other words, her whole course would fit tuberculous meningitis, except that she didn't die correctly for that disease.*

Pulmonary Vasculitis

In order to make tuberculosis the only diagnosis, one would still have to explain the abrupt death. In this regard there are several facts of interest which I found in obscure texts. For example, in miliary tuberculosis there is a pulmonary vasculitis, which has been well described by a number of different authors. Not entirely unheard of is death from tuberculous meningitis caused by a large pulmonary vein thrombosis with embolus, primarily from a fungating tuberculous mass originating inside the pulmonary vascular bed. However, that may seem like pulling one out of the hat, and I am not depending on it as a final diagnosis.

Sudden Vertebral Body Collapse

Furthermore, this woman may have died of tuberculosis from skeletal disease, unobserved by X ray or story, of the cervical or upper thoracic spine, with sudden collapse of her vertebrae and pinching of the spinal cord. This is hardly probable, however, because we can see that most of those portions of the spine were not diseased enough to collapse. Finally, a patient might die abruptly from tuberculosis if he had a hemorrhage in the lung or the brain or perhaps into the mass itself. But we have no evidence that this happened in the case we are discussing.

Syphilis

I might add too that syphilis could be responsible for the death. As a matter of fact, I spent a great deal of time trying to discover a relationship between the mass here noted and a large gumma, which not infrequently hits the liver; but I could not find that a gumma grows this big or becomes calcified. However, a gumma, followed by central nervous system disease such as syphilis, pachymeningitis, or meningo-encephalitis, was not, in the past, an uncommon disease. Furthermore, the clinical story as described here could very easily fit luetic central nervous system disease with meningitis, the focus being the usual venereal disease with a gumma. This is not an unheard of combination of events. But without the serological test for syphilis, one really cannot even consider such a diagnosis; for with both central nervous system disease and gumma, there is always a high titer serological test for syphilis. It is never negative; this is true both of blood and of spinal fluid with or without prior treatment. If this patient had a gumma, it is evident that she did not get adequate treatment in the past, because gummas respond very well to penicillin. It is also true that with small amounts of arsenic, bismuth, or penicillin the serological test would not revert to normal; consequently, I think we have to exclude the possibility of syphilis of the central nervous system with gumma in the abdomen, probably attached to the liver.

Abdominal Masses

In the abdomen in the area of the right kidney one can enumerate 81 causes of masses. I have restricted myself to three of these for discussion here.

The first, because of the classification and the description in the protocol, is a cystic component. The *Echinococcus cyst* of hydatid disease I ruled out very promptly. Sheepherders' disease, found only in Eastern Europe, may appear in immigrants coming to America, but not in an American Negro. *Mesenteric cysts* not infrequently do occur at age 60 and are found twice as often in the female as in the male. They can be of any size and due to a number of different causes: a healed hematoma, a large abscess with healing, a broken-down lipoma with healing, or just a major hemorrhage from known hypertension. They can become calcified, fibrotic, and also hard and nonpainful, as in this case. Furthermore, at the end they can rupture, followed by shock and rather sudden death — "G.I. apoplexy," if you will. But this mass actually is too big to qualify as a mesenteric cyst. One must remember that this mass is two and one-half times the size of a grapefruit, while cysts of the mesentery generally are fist size. Therefore, on this basis, I would suggest that mesenteric cyst formation could not explain the whole phenomenon; furthermore, if such a cyst had lead to hemorrhage and death, there ought to have been some data to the effect that at the terminal stage, the patient went into shock and became cyanotic with a weak and thready pulse. However, this is not recorded.

The third disease to be considered is *renal cyst or carcinoma,* which on first observation, I immediately excluded because there was no evidence of hematuria, and I do not know of any case of renal carcinoma in which hematuria is not a major symptom. Furthermore, this patient did not complain of pain of any kind during the history or during her last hospital stay. A renal cyst conceivably would be a better bet, since such cysts apparently can get bigger than carcinomas. They can also be solitary. They arise in the lower pole. They can heal. They can get infected. They can become fibrotic. They can get encapsulated. And they can become calcified. Like the cysts in the mesentery, they can follow abscesses or hemorrhages or even tuberculosis. I suppose, however, that there are a thousand other things in the abdomen which could cause a mass this size. For example, I learned this morning, only an hour ago, that a neuroblastoma could produce such a mass; in that case, I do not apologize for missing it.

Pulmonary Embolism

Finally, as to the suddenness of this woman's death: sudden death is hard to explain. It has to be due to a catastrophe of some type related to

Continued

the heart or to the aorta near the heart. Now I would presume that this patient did not really die suddenly, but, unable to breathe well, sat up for a while before expiring. This delay excludes abrupt death automatically related to the heart. From the very first I considered that the patient had a pulmonary infarct or perhaps a major embolus involving one of the principal pulmonary vessels. It would have been more conclusive to have this diagnosis confirmed by observation and clinical records. Patients dying this way usually suffer pain. They have dilated pupils and protruding eyes. They become cyanotic. They have large, swollen cervical veins and then go into shock before they die. In this case, sudden death could have been caused by a fungating tuberculous mass in the pulmonary artery. More likely, the embolus arose secondary to the effects of the huge abdominal mass.

To summarize: I make three tentative diagnoses: (1) The patient had tuberculosis with diffuse miliary disease and meningeal tuberculosis. However, after three months' duration, this disease should have been easy for the pathologist to diagnose, because of the varying ages of the lesions. (2) She had a renal mass — either a cyst or a carcinoma — with calcification, and perhaps hemorrhage as a terminal event. This diagnosis would explain the urine findings. (3) She had a serious case of pyelonephritis, eventuating in pulmonary embolus or thrombosis, and perhaps in tuberculosis by embolus from the mass.

Dr. Robert F. Rohner*

The Pathologic Findings

If all of our clinicians were like Dr. Bunn, we'd have very dull autopsies indeed, because we have nothing to surprise you with except a fibroid! In presenting a CPC, it is always disappointing not to be able to 'kill' the patient more satisfactorily.

Embolus

Dr. Bunn 'killed' the patient with an embolus, and this is exactly what the patient had. Nestled within the pulmonary artery of the left lung was a big embolus; to prove its antemortem structure, we could see the lines of Zahn passing nicely throughout. The mode of exodus is confirmed. There is no problem.

Now that we've 'killed' the patient, we can discuss the niceties of the case. Sections of the patient's heart show, within the myocardium, granlomata of recent origin. These have histiocytes with epitheloid changes and Langhan's type giant cells. Were these in the septum, near the conducting mechanism, we might have 'killed' the patient with an acute arrhythemia, but they were located in a random fashion in the lateral aspect of the left ventricle.

The Lungs

On sectioning the lungs, scattered throughout the parenchyma bilaterally, we found multiple small grayish opalescent dewdrops, the tubercules from which tuberculosis gets its name.

In all of the lung sections, we find the same general picture, in which the lesions are becoming confluent, but are all of the same general age. They have the appearance of the classical loose tubercle with a loose conglomeration of macrophages and some caseation. In the right apex there is a three-cm. area more densely infiltrated than the rest of the lung. Slide 1 shows this portion of the lung with a rather loose aggregate of histiocytes and a little fibrosis. This lesion is still very recent in its development.

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*Assistant Professor of Pathology, State University of New York.

The Spleen & Liver

In the spleen, the reticulo-endothelial system does indeed filter out foreign material, and the tubercle bacillus organism constitutes foreign material. In the spleen, we found multiple tubercles, all at the same stage of development and identical to those in the heart and lung.

The liver, another reticulo-endothelial organ, has nice miliary tubercles of the same age as those in the other organs.

The Adrenal & Kidneys

The adrenal has a peculiar sensitivity to tuberculosis, as we all know. Slide 2 shows a tubercle within the adrenal parenchyma, of about the same age as the tubercles located elsewhere. In the adrenal, this could develop into a progressive disease. In the spleen or liver progressive disease is unusual. The cellular lipid component of the adrenal cortex is markedly depleted, indicating that this woman has been under severe stress during the last several months.

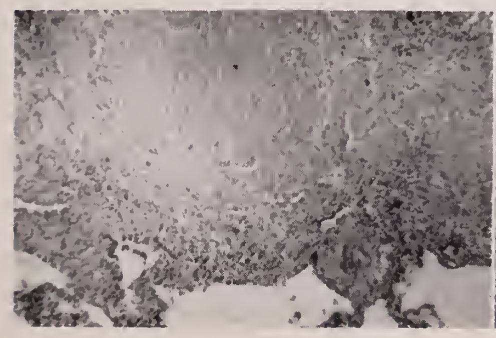
Both kidneys were rather markedly involved with multiple caseating foci involving both cortex and medulla. We found good fibrous reaction around them. The difficulty probably arose from a spread from the kidney, the second most common site, as Dr. Bunn told you, the first site being the bone.

Pedunculated Calcified Leiomyoma

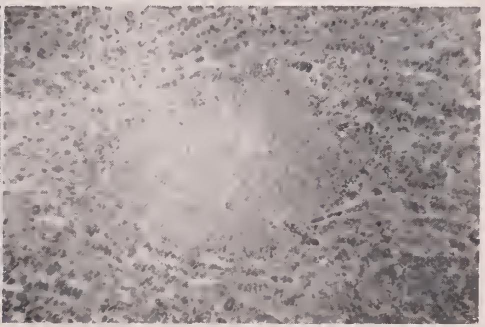
Attached to the right fundus of the uterus was a pedunculated 15-cm., hard, partially calcified leiomyoma with central hyaline degeneration, but no real cystic component.

Nervous System

One of the peculiarities of tuberculous meningitis, as we have seen it lately, is that it is hard to recognize grossly. We can observe a very small amount of thickening near the optic chiasm — a little dullness and granularity, but not very impressive. Many times this thickening comes as a surprise to us when we get our microscopic sections back.



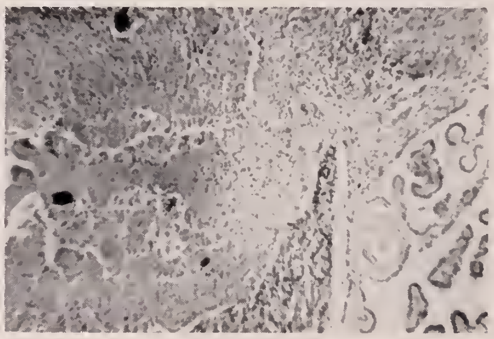
Slide 1 — Lung Section



Slide 2 — Adrenal Section

In the brain sections we found a diffuse granulomatous reaction in the leptomeninges extending down between the convolutions into the sulci of the brain. This is, indeed, a tuberculous leptomeningitis. Bulging into the lateral ventricle of the left side of the brain was a typical tuberculoma extending down from the brain tissue to involve the choroid plexus. Here we have a massive seeding of the meninges which are usually rather resistant to tuberculosis.

The next slide (Slide 3) shows the choroid plexus being heavily infiltrated. We can see coagulative necrosis, leaving us just the histological preservation and the cytological obliteration of acute degeneration. Of course, the choroid plexus is a vascular organ and a fertile focus to seed into the blood stream for miliary spread.



Slide 3 — Section of Brain and Choroid Plexus.

Our sections of bone showed only acute focal miliary lesions.

Microscopically we had no trouble finding the "red snappers," which were present in generous numbers in our acid-fast stains of the brain, kidney and lungs.

The pathology is left exactly as Dr. Bunn explained it, with the exception of the leiomyoma of the uterus. This woman's primary disease undoubtedly started in the kidneys and subsequently disseminated to involve the brain, with a rupture of a tuberculoma into the lateral ventricle, producing a meningitis involving the choroid plexus and in all probability seeding the rest of the body with miliary spread. Her pulmonary embolus we attribute to the fact that she was sick in bed, with a mass pushing on her inferior vena cava; and with a decrease in clotting time and a sludging of the blood flow, she was perfectly entitled to develop a thrombophlebitis. More exactly, we should term it a phlebothrombosis with a terminal pulmonary embolus.

Pathological Diagnoses:

1. Miliary tuberculosis
2. Tuberculous meningitis
3. Chronic renal tuberculosis
4. Pulmonary embolism
5. Leiomyoma uteri

Anthony Voytovich*
Joseph A. Head, M.D.**
Paul A. Bunn, M.D.***
Robert F. Rohner, M.D.†
Syracuse, N. Y.

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Advances

Current Status of Antimycotic Agents Having Systemic Effect

WILLIAM J. MARTIN, M.D.*
Rochester, Minnesota

IT IS WELL to recall that in certain mycotic infections which may cause generalized bodily involvement, therapy with amphotericin B is not applicable, or at least is not to be initially considered. These mycoses and the preferred regimens are the following: (1) actinomycosis, in which penicillin usually is satisfactory and in which tetracyclines also have been effective,[1] (2) nocardiosis without involvement of the central nervous system, in which sulfonamides are efficacious;[2] in similar cases refractory to the sulfonamides cycloserine has given encouraging preliminary results,[3] (3) certain cases of South American blastomycosis, in which sulfonamides are effective, (4) selected cases of North American blastomycosis, in which the diamidine bases have been successful, and (5) sporotrichosis, especially of the more localized variety, in which potassium iodide may be satisfactory.

The first two drugs to be discussed below are being evaluated in mycotic infections which tend toward generalized involvement and which are not contained in the aforementioned categories. The remaining drug is used in certain mycotic infections of the skin and its appendages.

Amphotericin B

Amphotericin B[4,5] is proving to be an effective drug against deep-seated mycotic infections. Against susceptible yeasts and fungi, the drug is fungistatic rather than fungicidal. The agent is effective against cryptococcosis,[4] and preliminary data are encouraging on the use of the drug against certain other mycotic infections. In cases of cryptococcal meningitis, as least 50 per cent of patients are apparently cured after a single course of amphotericin B; an additional 30 per cent or so can be successfully re-treated, so that the over-all failure rate of treatment with amphotericin B may be in the neighborhood of 20 per cent.

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*Section of Medicine, Mayo Clinic and Mayo Foundation.

Continued

Indications for Use

Use of amphotericin B should be considered in certain cases of generalized North American blastomycosis, South American blastomycosis refractory to the sulfonamides, disseminated or chronic cavitary histoplasmosis, and coccidioidomycosis, aspergillosis, sporotrichosis, chromoblastomycosis, nocardiosis involving the central nervous system, disseminated candidiasis, mucormycosis and other mycotic infections wherein less toxic antimicrobial agents are ineffective.

Since it is more effective than stilbamidine or hydroxystilbamidine, amphotericin B has replaced the diamidine bases as the preferred regimen in management of selected cases of generalized North American blastomycosis. However, as aforementioned, in less serious forms of North American blastomycosis, the diamidines warrant a trial before resort is had to more cumbersome amphotericin B therapy. Preliminary clinical data indicate that amphotericin B is effective in cases of South American blastomycosis refractory to the sulfonamides. Amphotericin B has caused conversion of sputum in patients with chronic cavitary pulmonary histoplasmosis and has arrested and cured cases of severe, disseminated histoplasmosis, and has resulted in complete remission in persons having histoplasma meningitis. In the therapy of disseminated and meningeal coccidioidomycosis, amphotericin B has given variable results; in some cases there has been no response, and in others recurrences have necessitated several courses of treatment. Some cases of coccidioidal osteomyelitis have been arrested.

The agent warrants at least a clinical trial in patients who have nocardiosis involving the central nervous system, since in our experience the sulfonamides are ineffective in such cases; cycloserine may warrant investigation in these cases. Use of amphotericin B is indicated in Candida endocarditis complicating cardiac operations; however, since the presence of foreign bodies (sutures, prostheses) may be implicated in the genesis of the lesion, cardotomy with excision of vegetations and repair of any defect also may be required. Cephalosporium infections may resist the action of amphotericin B.[6]

At present there is no clinical evidence of acquired resistance to amphotericin B by previously susceptible micro-organisms.

Route of Administration

Since there is only minimal absorption of amphotericin B after oral administration, it is given intravenously for systemic infections. For intravenous administration, each milligram of the agent is dissolved in at least 5 ml. of a 5 per cent solution of dextrose in distilled water. Saline solution, which will cause the drug to precipitate, should not be used. Visible particles of the agent should be filtered out of the solution before administration or, better, the solution should be discarded; a filter of the type used in transfusion of blood may be placed in the apparatus delivering the medication as a safeguard against further precipitation. Prepared solutions that are not used within 24 hours should be discarded.

The drug is administered intravenously in a single daily dose which varies from 0.25 to 1.0 mg./kg. Treatment is begun with an initial dose of 0.25 mg./kg. of body weight. The rate of infusion is adjusted so that the dose is given over a six to twelve-hour period. Blood levels of amphotericin B may be detectable for as long as eighteen hours after its intravenous infusion has been discontinued, but daily infusions do not appear to result in a cumulative rise in such levels. The infusion preferably is given daily, but intolerance on the part of the patient may require reduction to every other day. Continuation of therapy for four to eight weeks is usual, but data are lacking to establish precisely optimal amounts of the drug or the duration of therapy. Some patients have received the drug for several months. Average total doses appear to have been 2 to 4 gm., but some patients have received 10 gm. and more. One attempts to increase gradually (in increments of 10 mg.) the amount of the agent being administered to approximately 1 mg./kg. of body weight daily, depending on the tolerance of the patient.

In general, coccidioidomycosis is more resistant to therapy than North American blastomycosis, cryptococcosis, and histoplasmosis, and it therefore requires more prolonged therapy. It is not known whether intraventricular or intrathecal administration of amphotericin B in combination with intravenous therapy is necessary for mycotic meningitis, but such may be indicated in those who have a relapse after previous intravenous therapy or who at the onset are seriously ill. The drug has been given as an aerosol, applied to cutaneous lesions, and injected intra-articularly and intra-pleurally as well as directly into subcutaneous tumefactions and areas of osteomyelitis. It might be given orally for intestinal mycotic invasion or involvement.

Complications

Phlebitis at the site of administration, arachnoiditis following intrathecal injection, flushing, chills, fever, headache, myalgia, anorexia, nausea, vomiting, dyspepsia, diarrhea, anemia, hypokalemia, respiratory distress, an anaphylactoid reaction with occasional peripheral cyanosis, diminished ability to concentrate the urine, proteinuria, microscopic hematuria, decreasing renal clearances, and azotemia may result from administration of amphotericin B. Fatal reactions to amphotericin B have been reported.[7,8] The majority of patients show increasing azotemia after prolonged therapy with higher doses of the drug, and this effect is the chief limiting factor in the doses which may be employed. Renal function tests should be made regularly during therapy. In our experience, administering the medicament over a longer time interval, decreasing the total daily dose, giving the drug on alternate days, and stopping treatment for a few days have each been effective in controlling most side effects.

Method of Administration

It is preferable to adjust the dosage and thereby to prolong the time of treatment rather than to use higher dosages that may be productive of toxicity, especially renal. When therapy is stopped for a period of days, it is resumed with a lower dose and increased gradually to the optimal level. Aspirin, antihistaminics, and epinephrine may help control some untoward reactions. Corticosteroids also have been recommended in this regard; the sodium succinate ester of hydrocortisone in amounts of 50 mg. has been given intramuscularly before or added to the infusion of amphotericin B. The hazards of using corticosteroids in patients having systemic mycoses are not known, but the potential danger is such that some investigators are loath to accept the use of these agents. Renal biopsies in patients currently or recently receiving amphotericin B have revealed tubular, interstitial, and glomerular changes. It appears that such morphologic changes occur even in the absence of azotemia. Renal biopsies from patients one month to one year following therapy with amphotericin B have revealed necrosis and calcification of tubular cells. Deterioration of renal function to the point of irreversible renal failure and renal transplantation has been described.[9] Early reports on amphotericin B indicated reversibility of renal dysfunction after use of the drug was discontinued, but with increasing experience it is evident that such does not invariably occur.

X-5079C

X-5079C (Hoffmann-La Roche[10-12]) is an antifungal antibiotic of polypetide nature which is soluble in water and can be administered subcutaneously. After subcutaneous injection, maximal plasma concentrations are attained in about one and a half hours with only slight decrease during the following four to five hours. Traces of the drug are detectable in the plasma 24 hours after a single injection. Within 24 hours, approximately 20 per cent of the injected amount appears to be excreted in the urine. The drug has shown beneficial effects in experimental mycoses in animals, and preliminary studies in certain fungal diseases in man are said to be encouraging. The drug is reported as having been beneficial in Histoplasma infections, and its use has been suggested in selected cases of North American blastomycosis, sporotrichosis, aspergillosis, mucormycosis, and maduromycosis. It appears to be ineffective in coccidioidomycosis and candidiasis.

Continued

Dosage

Doses of 4 to 8 mg./kg. have been administered daily for several months by the subcutaneous route. The usual daily dose is 200 to 300 mg. administered in four divided doses for four to five weeks.

Side Effects

Side effects of the drug have consisted of pain at the site of injection, delayed excretion of sulfobromophthalein, and increased concentration in the serum of direct-reacting bilirubin. Liver biopsies have revealed periportal inflammation. The evidence of apparent hepatotoxicity reportedly subsides within several days after administration of the drug has been stopped. Since some investigators have concluded that the hepatic dysfunction is benign and reversible, therapy with the drug has been continued despite its presence. However, pre-existing liver disease is considered to be a contraindication to use of the drug. Retention of sulfobromophthalein usually occurs about one week after therapy is begun, while hyperbilirubinemia commonly is noted after the fourth week of therapy.

The type and incidence of side effects have varied with different batches of the antibiotic. Certain batches have given considerable pain at the injection site but have had little effect on liver function tests, while the reverse has occurred with other lots of the agent. However, it has been difficult to manufacture this antibiotic in quantity, and consequently further investigational work with this preparation is not expected in the near future.[12]

Griseofulvin

Griseofulvin[13-15] apparently marks a major advance in the therapy of certain superficial fungous infections of the skin and its appendages. It is absorbed after oral administration, is excreted rapidly, and is fungistatic rather than fungicidal.

Indications for Use

Infections that may respond to griseofulvin therapy include tinea capitis, barbae, cruris, corporis, and pedis, as well as onychomycosis due to Trichophyton mentagrophytes, rubrum, schoenleini, sulfureum, verrucosum, and interdigitale, and those similar infections due to Epidermophyton floccosum or Microsporum gypseum, canis, and audouini. Results in management of tinea pedis are most likely to be unsatisfactory. Since the antimicrobial spectrum of griseofulvin is limited, therapy should not be instituted until the causative organism is identified. The use of griseofulvin is not justified in infections which respond readily to topical antifungal agents alone.

Method of Administration

In adults, griseofulvin in the microcrystalline form is given in amounts of 500 mg. two to four times daily. Patients with extensive lesions may require a starting dose of 0.75 to 1 gm. a day. Therapy should be continued at least two weeks after clinical signs of infection have abated and laboratory tests are negative for fungi. It is to be recalled that wearing apparel, such as hats and footwear, and other fomites, such as pillows, may be sources of reinfection.

The length of therapy in general depends upon the site of involvement, the severity of the infection, the response obtained, and acceptance of the regimen by the patient. The usual length in tinea corporis and cruris is two to four weeks; in tinea capitis and barbae four to six weeks may be required; and tinea pedis may take three to six weeks or longer to respond. Onychomycosis commonly demands four to six months or more of treatment. The drug is often more effective when topical preparations and other external measures are employed concomitantly. Clipping of the hair and nails may help remove any remaining viable fungi. Surgical removal of the nails with simultaneous administration of griseofulvin may shorten the period of therapy for onychomycosis.

Side Effects

Side effects of griseofulvin include paresthesia, serum sickness-like reaction, photosensitivity, heartburn, nausea, epigastric discomfort, and diarrhea. Urticaria and other rashes may require that the drug be withdrawn. A few patients complain of headache during the first week of therapy, and psychomotor inco-ordination has been reported. The latter may impair performance of routine activities, such as those involved in driving an automobile. Lethargy and fatigue, and, paradoxically, insomnia may follow use of the drug. Leukopenia has developed in an occasional patient and has disappeared with discontinuation of therapy; nevertheless, periodic blood cell counts during administration of the drug are advised. Albuminuria also has been noted. Since griseofulvin is derived from species of Penicillium, the possibility of a cross-sensitivity reaction exists. Treatment has to be discontinued in 2 to 3 per cent of patients because of side effects. Currently, the drug is not recommended for use during pregnancy.

Comment

As a generalization, there remain but few mycotic infections in which the physician is therapeutically helpless. However, the currently available antimycotic agents often are productive of untoward reactions, and the duration of therapy frequently involves months. Continued investigation is necessary in the search for less toxic, more rapidly effective drugs. While not all instances of a given infection are susceptible to the action of currently available antimycotic agents, the general decrease in morbidity and mortality is impressive.

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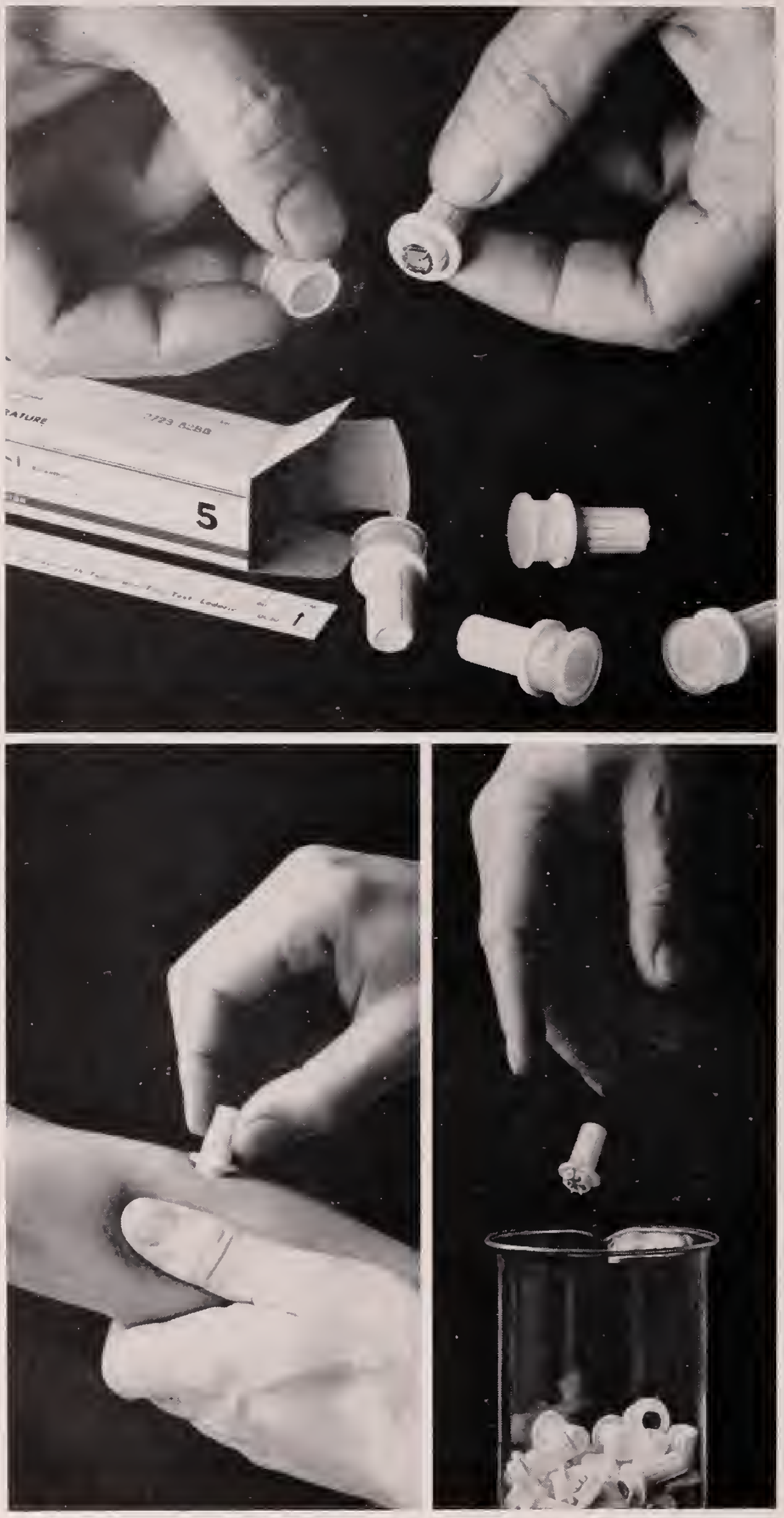
Remedy for Dizziness

Take a young swallow from her nest when the crescent moon is in Virgo; cut off the head and let the blood run into a vessel containing white frankincense; stir thoroughly until the fluid thickens; then give it to the patient when the moon is waning, three days in succession. But by all means see to it that the patient during the progress of the cure does not become angry at anything. — From a German "Artzneybuch" or Book on Therapeutics, published in 1596.

He who laughs frequently is kind and genial in all things and is not worried over trifles. He who laughs rarely is contrary and critical.

—Gilbertus Anglicus (Doctor Desideratissimus) (1180-1250)



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Grand Rounds

Tuberous Sclerosis*

Tuberous sclerosis is a condition with which few physicians have had personal experience unless associated with an institution for the mentally retarded. Most physicians, however, would recognize cases represented by the classic triad of retardation, seizures, and adenoma sebaceum. As with any disease process a wide spectrum of manifestations may be present, and the case to be presented is an example of the extreme in which diagnosis is possible only by the examination of pathological material. At the other end of the spectrum this condition has the potentiality of being a multi-system disease involving tissues derived from all three germ layers and from almost every organ system in the body. Many of these manifestations are not necessarily of direct clinical significance, but a study of them aids full understanding of the disease, directs the first step towards prevention and treatment, and serves as an aid to diagnosis. The necessity of an exact diagnosis is of the utmost importance because the disease is hereditary and the genetic implications raised by finding an afflicted child are obvious.

This review will attempt to cover the widespread manifestations of tuberous sclerosis in a comprehensive fashion after the presentation of a rather atypical case. The reviews of Ramakumar,[1] de la Cruz and la Veck,[2] and Chao[3] may be referred to for further details as well as historical information.

Case Report

The patient was first admitted to the University of Minnesota Hospitals in 1954 at age eighteen months for the evaluation of seizures. Nine months previously she had suddenly developed a staring expression, had become cyanotic and limp, and had fallen to one side. These episodes recurred frequently, and for two months she had also displayed jerking movements of her head to the right. There was no family history of mental retardation or seizures. Her developmental pattern was normal. She sat unsupported at five months, stood at six to seven months, said her first word at ten months, and walked at thirteen months.

Physical examination, routine laboratory studies, and lumbar puncture were all normal. Skull X rays showed no intracranial calcifications. Electroencephalogram displayed a spike and wave pattern. The patient was discharged on treatment with R Mebroin.

Follow-up was done by her family physician, and she apparently did well. Anticonvulsant medication was stopped in 1956 without return of seizures.

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*First presented as a Pediatric Pathology Conference, University of Minnesota.

Continued

During the winter of 1962-63 she suffered six episodes of nausea, vomiting and headache, and underwent a personality change, becoming more irritable. In February, 1963, she began to complain of pain in her hamstrings, and in March was seen to be walking with a peculiar gait, placing her toes down first. She also complained of pain in her back and inability to bend over. Studies in her local hospital were not diagnostic. She was transferred to the University Hospitals in July, 1963, for further evaluation.

A significant item in the interval was a considerable slowing of her mental development. At age four her tested IQ was 65 and she was enrolled in a special school. Physical examination showed her left pupil to react sluggishly to light. There was a five-diopter papilledema bilaterally but no retinal hemorrhages. Gross testing showed decreased vision in the left eye. Her neck and back were stiff with marked lordosis of the lumbar spine; her gait was spastic and somewhat broad-based. All extremities were hypertonic and deep tendon reflexes symmetrically increased. A mild, fine intention tremor could be demonstrated.

Routine laboratory studies were within normal ranges. Skull and spine roentgenograms showed spread of all sutures, a marked increase in digital convolutions and a lack of fusion of the neural arch of the lumbarized first sacral segment.

A ventriculogram was performed. A five by six cm. mass was found, occupying the floor of the left lateral ventricle and protruding across the midline to the right lateral ventricle. A transfrontal craniotomy was performed and a large, reddish, fairly well circumscribed tumor removed from the frontal horn of the left ventricle. This tumor had pushed the septum pellucidum to the right and compressed the third ventricle.

She did well until the third postoperative day when intraventricular bleeding suddenly began. She rapidly became decerebrate and remained in this condition. She was then transferred home for terminal nursing care.

Pathological examination of the tumor tissue showed many large bizarre cells arranged in an abnormal irregular fashion. The tissue diagnosis was astrocytoma arising in an area of pre-existent tuberous sclerosis. A cortical biopsy obtained during investigation of the sudden deterioration showed a focus of tuberous sclerosis cells within the otherwise normal cortex.

On a careful retrospective clinical examination of the patient none of the expected cutaneous manifestations of the tuberous sclerosis could be found.

Definitions

The term tuberous sclerosis remains as useful as any at the present time. Epiloa, a term suggested by Sherlock,[4] is only a contraction of the Greek words for "epilepsy" and "mindlessness" and has no real meaning in itself. The disease is also classified as belonging to the phakomas or neuroectodermal dysplasias. The term phakoma was first used by van der Hoeve[5] to refer to certain ophthamologic findings common to all these conditions; but this finding alone would make tenuous grounds for deriving a new nosologic category. Neuroectodermal dysplasia has also been used to denote tuberous sclerosis, neurofibromatosis, Sturge-Weber syndrome,* von Hippel-Landau syndrome, and recently ataxia-telangiectasia. As no real relationship between these conditions has been established and because the best evidence suggests that most of these diseases involve more than neuroectodermal tissue, such groupings serve no useful function either clinically or pathologically.

Incidence

Tuberous sclerosis is a fairly uncommon disease with a frequency of 1:30,000 in the general population and comprising approximately 1:300 admissions to state hospitals for the mentally retarded.[1] Despite this relative rarity, the prevalence of the disease is such that there are more than 6000 cases in the United States. The incidence may be higher in some European countries, but no ethnic group seems to be predominantly affected. Some series report an equal sex incidence; others, a predominance of males.[2]

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*See Minn Med. p 781, July, 1964.

Genetics

The inheritance of tuberous sclerosis is confusing, but the seemingly great variations in expressivity of the gene are as of now best explained by assuming the presence of a single autosomal recessive gene under the influence of a pair of codominant modifier genes.[6] In the chart below E(e) stands for the "epiloa gene" and A(a) for the modifier gene.

EE	Unknown significance
Ee — aa	Severely affected
Aa	Mildly affected
AA	Asymptomatic carrier
ee — aa	
Aa	Not affected; not carriers
AA	

(Modified from Marshall et al.[6])

Although the genetic control of the disease seems well established, one half of the cases have no family history and probably represent new mutations. The mutation rate is between 1:120,000 and 1:60,000 genes/individual/generation.[6]

Clinical Aspects

Seizures

Seizures and mental retardation are the two best known aspects of brain involvement. The seizures are rarely present during infancy and most typically begin between ages three and six years, although in one reported case they did not begin until age thirty-one.[2] A rare case with onset of seizures in the first few months of life has also been seen. The seizures may assume any character, but most often are of major motor type. Focal seizures are unusual, except in case of superimposed malignancy. Postictal paralyses are likewise uncommon. Although convulsions are frequently difficult to control with routine drug therapy, occasional spontaneous remissions make evaluation of treatment difficult.

Mental Retardation

Mental retardation is usually quite severe, but patients with normal intelligence have had tuberous sclerosis documented by post-mortem examination. Severe behavior disturbances are frequent, which may be almost psychotic in character. Combined with the severely retarded intellect, this eventually leads to institutionalization in the majority of these patients.

Neuropathological Aspects

Brain

The neuropathology has been very clearly described by Greenfield.[7] The brain is grossly normal except for the presence of pale, stony-hard areas in the cortex. Microscopically these areas show an enormous increase in astrocytic nuclei and contain groups of very large bizarre cells which are pale-staining, have cytoplasmic vacuoles, and often show several nuclei with nucleoli. Most of these areas are in the cortex, but there may be heterotopias in the white matter and occasionally in the cerebellum. Diffuse fibrillary gliosis and atypical astrocytes may also be seen. Intraventricular or thalamic tumors consisting of round or oval cells with whorls

Continued

of dense fibrillary glial tissue are also found, often containing calcium. These calcified tumors are responsible for the periventricular calcifications seen on X ray.

Intracranial Tumors

Complications of intracranial tumors are of two types. First, the intraventricular tumors described above may obstruct the flow of cerebrospinal fluid, especially at the level of the aqueduct, and cause an acquired noncommunicating hydrocephalus. Second, neoplastic lesions may arise in areas of tuberous sclerosis. This complication, which occurred in the case presented, has been relatively frequently reported. The types of tumors found have included astrocytomas (especially intraventricular), glioblastomas, spongioblastomas, ependymomas, and gangliogliomas. The latter may be massive and infiltrate an entire hemisphere.[8] An intraventricular brain tumor should always suggest the possibility of tuberous sclerosis.

Other Pathologic Aspects

Skin

Adenoma sebaceum is one of the classic cutaneous lesions of tuberous sclerosis. This consists of pink to red glistening tumors arranged bilaterally symmetrically on the face, especially in the "butterfly" distribution. They sometimes involve the forehead and scalp, but almost always spare the upper lip, giving a relative circumoral pallor. These lesions occur in 90% of cases, usually between ages five to thirteen. Many appear at the time of puberty, but one reported case had the first signs only at age twenty-six. On rare occasion they are present at birth. Microscopically an overgrowth of sebaceous glands, connective tissue, and blood vessels is seen.

Many other cutaneous lesions have been associated with tuberous sclerosis. Multiple soft, pink, doughy fibromata on the scalp and forehead may be present. Unlike adenoma sebaceum, these tend to be unilateral. When present at birth they provide one of the few manifestations of tuberous sclerosis detectable in the period of early infancy.

Shagreen Patch

A shagreen patch (peau de Chagrin) when present is nearly diagnostic. These patches are rough, flat, irregular, elevated plaques most generally found in the lumbar or lumbosacral areas. They may be single or multiple, and are classically described as being the size of the palm of the hand, but may be larger or smaller. The lesion is the same color as the surrounding skin or somewhat paler, and gives the impression of having longitudinal corrugations. Histologically these are avascular plaques of connective tissue within the skin and free from the deep structures.

Subungual Fibroma

Another pathognomonic finding is the presence of subungual or paraungual fibromas, which are found more frequently on the toes, often at the free edge of the nail, and consist of a mixture of fibrous and angiomatous tissues.

Other skin lesions described have included vitiligo, poliosis, skin tags, portwine hemangiomas, and cafe-au-lait spots; but these findings are frequent enough in the general population to cast doubt on their diagnostic significance.

Eyes

Examination of the eyes may be very helpful.[10] Externally visible small grey-white nodules may be present on the lower tarsal conjunctivae in symmetrical distribution.

Two major types of retinal lesions may be present. Small, yellow, flat nodules can be seen on any part of the retina and may be single or multiple. Histologically these involve the nerve layer of the retina and, although they appear to be made up of primitive cells, probably never become malignant. The other type of retinal lesion is a large mulberry-like nodule projecting from the region of the disc forward into the vitreous humour. These lesions may be cystic, and, although they are usually avascular, a stalk of blood vessels sometimes projects into them for a short distance, and they may "metastasize" by breaking and seeding other intraocular structures. It is this type of finding that is common to the other "phakomatoses."

Papilledema may be caused by increased intracranial pressure due to a tumor obstructing the flow of cerebrospinal fluid or by direct involvement of the optic nerve with tumor. Optic atrophy may be seen as a result of previous papilledema or nerve infiltration. Other optic lesions include aneurysms of the ophthalmic artery, retinitis proliferans, retinitis pigmentosa, and nonspecific retinal pigmentary changes. Despite this variety of ophthamologic findings, clinically impaired vision is very unusual except when there is pronounced optic atrophy.

Mouth

In 15% of patients fibromas of the gingivae and occasionally of the palate and tongue can be found. Hyperplasia of the gingival sebaceous glands may also be present.[11]

Kidney

The kidneys are affected in 80% of patients with tuberous sclerosis.[12] Single or multiple cysts or nodules may be present and give X-ray or clinical findings similar to those of malignant renal neoplasms. In fact, malignant changes can develop in such tumors at any age. The patients are generally asymptomatic, but some have hematuria renal pain or a history of repeated urinary tract infections. Uremia is very rare and has been found only in some patients who survive to older ages. Pathological examination shows whitish-yellow nodules or cysts located in the renal cortex and measuring up to two cm. in diameter. Microscopically they represent a mass of spindle-shaped cells with elongated nuclei.

Bones

Osseous involvement is found in 60-65% of patients.[13] Roentgenograms of the hands and feet may show small areas of rarefaction or irregular subperiostial bone formation. The skull frequently displays hyperostosis of the inner table of its petrous portion. Long bones have irregular cortical thickenings and cysts. The rarest manifestations are in the spine, ribs, and pelvis which may in an occasional case show extensive focal and confluent sclerotic lesions. Aside from other associated bony abnormalities such as

Continued

syndactaly, polydactaly, and spina bifida, osseous lesions are usually asymptomatic.

Heart

The rare condition of congenital rhabdomyoma is, when present, characteristic.[14] There may be solitary or multiple subendocardial tumors or diffuse involvement of the whole myocardium with a loose network of interlocking fibrils and large rounded bodies with eosinophilic cytoplasm. These structures appear like, and are felt to represent, fetal Purkinje cells. The characteristic appearance on histologic section resembles a spiderweb, and the cells have been called by this name. In the past it was considered that the large volumes of eosinophilic material represented glycogen; but recent studies suggest that it may be a different though possibly related polysaccharide. These subendocardial tumors may cause sudden death in infancy; later in life they stop growing, fibrose, and calcify. These tumors have never been reported to show malignant change or to metastasize. Most cases of congenital rhabdomyoma of the heart have occurred in patients with tuberous sclerosis.

Lungs

Pulmonary involvement is one of the rarest manifestations of this disease and occurs primarily in women in the third decade of life.[12] The youngest reported patient was a woman aged 24. Clinically these patients present with progressive dyspnea, hymoptysis, or spontaneous pneumothorax. Roentgenograms display a widespread reticular mottling with focal thickenings that may resemble the picture of pulmonary sarcoidosis. Death from pulmonary insufficiency generally occurs within five years of the onset of symptoms.

Pathologically the parenchyma is occupied by cystic spaces lined with flattened epithelial cells and separated by septa containing muscle-like cells, normal alveoli, and iron pigment. These cysts are both parenchymal and subpleural. The subpleural cysts may rupture — in one third of the patients — and cause spontaneous pneumothoraces.

Other Organ Systems

Fibrocellular tumors may also be found in the thyroid, liver, duodenum, adrenal and ovary,[7] but these have never been reported to be of any clinical significance. Willis reports polyps of the large and small intestines.[15]

Laboratory Findings

Routine laboratory studies are normal except in the presence of superimposed disease processes. Electroencephalography is not often helpful. A diffuse abnormality is the common finding; however, a strongly focal recording has the same significance as focal seizures, suggesting a superimposed neoplasm. An electrocardiogram is usually normal, even in the presence of a rhabdomyoma.

Roentgenograms are of some assistance. Plain skull films may show the fairly characteristic multiple, small, discrete paraventricular calcifications. Bony changes in the skull, the long bones, the hands and feet, and rarely in the spine and pelvis may be present, as previously mentioned. Intracranial or bone changes are present in 85% of patients. Pneumoencephalogram often shows cortical atrophy, a nonspecific finding, but also may outline the "candle-guttering" pattern caused by the small fibrous tumors hanging into the ventricle.

Prognosis

The duration of life is usually shortened by the progressive changes in the multiple organ systems involved in this disease. Thirty per cent of the patients are dead by age five, 75 per cent by age twenty. The course is generally shorter in those with early onset of symptoms and those with the most severe retardation. Death due to manifestations of the disease process itself may be caused by status epilepticus, cachexia, and repeated infections in the severely retarded children; uremia occasionally; rhabdomyoma causing sudden death in infancy; and pulmonary insufficiency in an occasional adult female. Complications of the disease having a fatal outcome would include increased intracranial pressure due to blockage of the fourth ventricle, malignancy arising in the brain, or a renal tumor.

Treatment

There is no treatment available at the present time. The patient must be treated symptomatically and complications of the disease managed as they arise. Institutionalization depends on the patient's intelligence, the severity of behavior problems, and the family situation. The decision is one that must be reached by the parents. The physician's role in guiding and supporting the parents is the same as with any other severely retarded child.

Comment

Tuberous sclerosis is easily diagnosed in the presence of seizures, mental retardation, and adenoma sebaceum; however, the many variations in the clinical spectrum may make diagnosis difficult. In some cases, e.g., the case presented, the disease can be suspected clinically and proven only on histologic examination. In such cases the clinician is hampered by the multiple but inconstant manifestations and the fact that there is no really diagnostic test. Amino-acid chromatography, chromosome analysis, and other highly specialized laboratory tests, as well as the more common ones, have all been normal. Roentgenograms may be suggestive but are rarely diagnostic. The atypical cases and formes frustes of the disease will be discovered only if the diagnosis is considered and its varying manifestations carefully searched for.

Making an exact etiologic diagnosis in the retarded child is more than just an interesting intellectual exercise. The condition under discussion is hereditary and in 50% of the cases one or more other afflicted children may be expected in the family. A family history of the most carefully detailed type must be obtained and if the case in question seems to be familial, genetic counseling should be offered to the parents.

The need for careful diagnosis in mental retardation is important from another aspect. At the present time a few conditions exist in which early diagnosis and treatment mean the possibility of prevention of retardation or at least some protection of intellectual function. Hypoglycemia, hypothyroidism, and phenylketonuria are examples of such conditions. Tuberous sclerosis does not yet fall into this category, but may some day.

Continued

Summary

Tuberous sclerosis is a hereditary disease classically characterized by seizures, mental retardation, and adenoma sebaceum. The disease may involve almost any organ system. The clinical and pathological aspects of involvement of the brain, skin, eye, mouth, kidney, heart, bones, and lungs have been presented in some detail. Many cases may not exhibit all of the typical characteristics.

A plea is made for every attempt at an exact etiological diagnosis in all cases of mental retardation in order that proper treatment may be started and appropriate genetic counseling offered.

Gerald S. Golden, M.D.,*
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Flying Saucers

When it comes to flying saucers, some realists report that they can see saucers best when they are in their cups.—Harlow Shapley

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When man is no longer anxious to do better than well, he is done for.—Haydon

Abstracts, Briefs and Commentaries

CASTRATION IN BREAST CANCER

In recognition of the hormonal factors in growth of neoplasms of the breast, oophorectomy has been employed in the management of this disorder in premenopausal women. Uncertainty exists as to whether the patient benefits most from "prophylactic castration," i.e., that done as part of the initial therapy of the breast cancer, or from "therapeutic castration," i.e., oophorectomy employed if and when a recurrence develops. Literature supporting both approaches is reviewed.

The present study is an attempt to critically compare the effect of prophylactic castration in terms of total survival time with a comparable group of patients in whom oophorectomy is postponed until metastases are manifest.

A series of 296 patients having prophylactic or therapeutic castration for breast cancer was obtained from study of 2,908 patients with breast cancer treated at University of Minnesota Hospitals from 1909 to 1961. Of these, 119 had prophylactic castration and 177, therapeutic castration.

Intervals in months were determined for initial therapy to recurrence, recurrence to death, and initial therapy to death for the two groups.

The numbers of patients in the groups allow statistically significant comparisons. The data reveal that the two castration groups were homogeneous regarding age, site of primary, menstrual status, technic of castration, association with pregnancy and present state of patients. There was, however, a disproportionately larger number of inoperable (clinical Stage III or IV) patients in the therapeutic castration group.

A truly homogeneous group was then compared, selecting for analysis the clinical Stage I and II patients in the two castration groups. This resulted in the study of 108 prophylactically castrated patients and 105 therapeutically castrated patients.

Statistical analysis suggested that prophylactic castration may delay the onset of recurrent disease. The interval between initial tumor therapy and death was not different, however.

It is suggested that the term "prophylactic" castration is a misnomer since it does not prevent recurrence of breast cancer. The authors believe the terms "early therapeutic" and "late therapeutic" are more appropriate.

Robert N. Hammerstrom, M.D.
Minneapolis, Minn.

Kennedy, B. J., Mielke, P. W., and Fortuny, I. E.: Therapeutic Castration Versus Prophylactic Castration in Breast Cancer. S G & O 118:524, 1964.

Continued

METASTASES TO CERVICAL LYMPH NODES

In order to ascertain the value of limited resections in the neck area, the author has studied block dissections in 19 patients with squamous carcinoma of the oral cavity. A careful dissection and plot of the distribution of the nodes and their involvement with tumor have been studied. The significant finding in this study was the irregular nature of deposition within nodal groups. Some 30 percent of the specimens reflected moderate activity but revealed some unprecedented nodal metastasis manifest by involvement of distally situated nodes with omission of some of the more proximally located groups lying more directly in the pathway.

The author speculates that the skip involvement is a consequence of irregular anatomic lymphatic connections rather than a widespread embolization. He therefore concludes that the evidence favors the performance of radical excision of the lymphatic territory as against performance of conservative resections such as those involving only the supra-hyoid or supra-omohyoid areas.

A study of this kind is of particular value in that the author has found that in cases of only modest nodal involvement, the skip area affection is then discovered.

J. H. Strickler, M.D.
Minneapolis, Minn.

Toker, C.: Some Observations on the Distribution of Metastatic Squamous Carcinoma Within Cervical Lymph Nodes. Ann Surg 157:419, 1963.

SMALL TUMORS OF THE COLON

There is often uncertainty as to the course of action the surgeon should adopt when confronted with a patient in whom the radiologist identifies a small tumor in the colon. A diagnosis may be established if the lesion is within reach of the sigmoidoscope. In the colon, however, an abdominal approach is required to solve the problem.

The authors reviewed 1856 lesions in 1335 patients from Presbyterian Hospital in New York in the attempt to determine what the chances are that such a lesion of the colon may be an invasive malignancy, and if so, what the chances are that it may have metastasized to the regional nodes. They feel that size of the lesion may be the most important observable determining factor.

The study lists the incidence of malignancy in tumors of various size and analyses the incidence of node metastases in those where malignancy is found. The data suggests that, in an otherwise healthy person, a tumor of the colon one centimeter or more in diameter is a greater risk from the standpoint of death from cancer, than is the risk of removal. A tumor less than one centimeter in size may be justifiably observed at intervals for enlargement.

Lymph node metastases were found with malignancies 1.5 cm. and larger. Therefore, resection should be the usual procedure of choice with the possible exception of a pedunculated polyp of the rectum containing focal surface malignancy. In such an instance local excision may be acceptable.

Robert N. Hammerstrom, M.D.
Minneapolis, Minn.

Grinnell, R. S.: The Chance of Cancer and Lymphatic Metastasis in Small Colon Tumors Discovered on X-ray Examination. Ann Surg 159:132, 1964.

TOXIC EFFECT OF TOBACCO

The essential part of all tobacco enjoyment is the blocking and stimulating effect of the nicotine on the ganglions. The habitual smoker adapts the nicotine intake according to his changing tolerance and ever changing technique of smoking. From a single cigarette, for instance, an average of 2.5 mg. of nicotine is taken into the body, although the intake can be ten times more or ten times less by the unconscious changing of one of many factors of the technique of smoking.

The mucous membranes of the upper and lower respiratory passages react differently to the various ingredients of tobacco smoke. The main differences are: (1) The upper respiratory passages absorb practically no carbon monoxide, though the lower area absorbs 100%. (2) The resorption of nicotine in the upper respiratory passages amounts to about 10%, the lower ones to about 80%. (3) The industrial toxicological experiences show that the upper breathing passages are considerably less sensitive to the carcinogenetic effect of tar fumes than the lower respiratory system.

Absorption of Nicotine

When smoking cigars or pipes, the mainstream contains much nicotine, though resorption in the upper respiratory passages is enough to satisfy the nicotine craving. Those who wish to satisfy their nicotine hunger by cigarette smoking (one cigarette = 1 gram tobacco) must resorb nicotine in the lower lung passages; they must inhale deeply. The mode of smoking allows not only arsenic but also other carcinogenic substances in the tobacco smoke to be inhaled, thus setting the stage for the development of the "smoker's cancer," which is a "contact cancer."

The depth of the inhalation and thus the resulting individual danger of developing cancer can be evaluated by determining the carbon monoxide hemoglobin (carboxyhemoglobin) of the blood.

Carcinogens

The mainstream of smoke contains four carcinogenic substances: arsenic, chromium, nickel, and tar. That arsenic can produce skin cancer is shown by industrial surveys. An increase of lung cancer in workers handling arsenic has been reported particularly by Hueper.[1] Noteworthy is the occurrence of carcinoma of the nasal passages in nickel workers. The frequency is about 200 times more than carcinoma of the pulmonary system, which is only about 10 times increased. Pulmonary carcinoma caused by chromium is said to be 40 times greater. However, there is still much controversy regarding the carcinogenic action of trace metals.

With respect to the carcinogenic action of tar, it is known that the mainstream of smoke contains about 17.8 mg. of tar. A smoker who consumes 20 cigarettes a day inhales about 356 mg. of tar. Workers handling tar or exposed to tar fumes have a death rate 10 to 15 times greater from bronchiogenic carcinoma as compared with the general population and the same age groups. It is noteworthy that the mucosa of the mouth, throat, and nasal areas are less subject to tar-induced carcinoma than the bronchi, thus showing clearly the reason for the high incidence of bronchiogenic carcinoma in cigarette smokers who inhale. The time for the development of the latter is between 10 to 15 years, the same as for tar workers.

Cigarette vs Pipe vs Cigar

The difference in nicotine intake between the cigarette, pipe, and cigar is evident only in the cigarette smoker who wishes to obtain satisfaction from one cigarette and finds he must either smoke very rapidly or inhale deeply in order to obtain a large amount of injurious material to the bronchial mucosa. Cigar and pipe tobacco contain about the same amount of nicotine as the cigarette, but the absorption is less because of the tendency to eliminate deep inhalation of the smoke. If the cigar and pipe smoker should inhale, as does the cigarette smoker, an acute nicotine poisoning would result in the same manner.

The smoking time of a cigarette is about 10 minutes, with an average of ten "drags." One drag continues from 0.5 to 4 seconds resulting in an intake volume of 20 to 60 cm^3. The suction pressure alternates between 50 and 400 mm. of water. If a cigarette is smoked in five minutes instead of over a period of ten minutes the main smokestream contains approximately ten times more nicotine. It is noteworthy that one third of a cigar contains 24 mg., the second third 29 mg., and the third portion gives up 46 mg. of nicotine. Thus, the mode of smoking, the length of the cigarette, cigar, pipestem, quantity of tobacco, smoking time, character of suction, drag, and the degree of inhalation influence the nicotine content of the main smokestream. An average of 2.5 mg. of nicotine is taken into the body during the smoking of one cigarette in ten minutes; and about 10 mg. is taken in from a cigar during one hour of smoking. Though smoking 20 cigarettes a day represents about 50 mg. of nicotine, it is said that 10% of nicotine is eliminated by the kidneys and 80% by the liver.

In summary, we are convinced that deep inhalation is directly and causally related to "smoker's cancer." The carbon monoxide hemoglobin determination of the blood should prove to be a practical method for an early detection of the degree of deep inhalation and also as an individual danger signal of the development or presence of a hypersensitive individual and the possibility of subsequent smoker's cancer.

Emil Schleicher, M.D.
Minneapolis, Minn.

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TYMPANOPLASTY IN CHILDREN

Cholesteatoma was found in 58% of 564 children operated on during a seven-year period for otitis media. Cholesteatoma grows deeply into the pneumatic system of the mastoid process in children, making extensive operation necessary. Radical operation was performed on 317 patients, conservative atticotomy in 89, and tympanoplasty (one-stage) in 219. Of these 219 patients, 122 were cholesteatomatous. Improved hearing was achieved in 51% of those operated with cholesteatoma and in 73% of those without cholesteatoma. Socially useful hearing was obtained in 108 cases (50% of all tympanoplasties). A large operative cavity is slow in healing. Tympanoplasty should be done in two stages.

Courtesy of References and Reviews
Journal of the American Medical Association

Gans, H.: Arch Otolaryng 77:350, 1963

CLOSED ABDOMINAL INJURIES

Closed abdominal trauma is becoming increasingly common. This study is based on a review of 242,252 patients admitted to the general infirmary at Leeds, England. Of these, 248 were admitted as having potential abdominal injuries, together with 17 patients admitted under another diagnosis and found to have an abdominal visceral injury. This percentage was 1 in 1977 admitted patients. The younger age, five to nine years, had a greater percentage of abdominal injuries than the age 10 to 14 group of school children. The most frequently involved were young males, 15 to 24. Those over 65 years of age surprisingly revealed more than twice as many women as men. Percentages showed that 36.2% of the total were road accidents; 20.8% were work accidents; 17.4% were sport and play accidents.

Different reports vary considerably, based on statistics in other hospitals in different areas. Road accidents productive of abdominal injuries were 60% in Birmingham, 61.5% in New York, and 53% in Michigan.

Cases were reviewed with regard to injury to one organ, multiple organs, abdominal wall, and those where the final diagnosis was not confirmed. The liver, though the largest organ, is more protected and less often involved than other organs. However, liver damage is more serious and the mortality from liver damage alone was 30%; but it was 80% when more than one viscus was involved. Glenn stated, in regard to the prognosis of liver injuries: "One third will die at the site of the accident, one third will die within six hours, and one third will survive." Generally, the mortality rate has improved in recent years and a mortality of 4% has been reported in 25 cases.

Injury to the spleen is often produced by only slight trauma to the left lower ribs. The interval between injury and the presence of symptoms varies and emphasizes the importance of observation of patients who have had left upper abdominal trauma, even if slight. Hemorrhage may be delayed for days and suddenly, with a profuse blood loss, become critical after the primary injury has been forgotten. The author reports a twenty-year-old University student who was injured in a motorcycle accident and, after being observed for three days, was permitted to go home. Two days later he had sudden pain in his abdomen and left shoulder. He became weak, short of breath, and progressed into shock. He was returned to the hospital and a laparotomy was performed. Three or four pints of fresh blood were found in the abdominal cavity and an organized hematoma at the upper pole of the spleen. Recovery was prompt after splenectomy.

All patients with gastrointestinal lesions due to trauma demand prompt surgery. The presence of multiple injuries often confuses the picture. One case was having orthopedic surgery for fractures when the abdominal pathology was discovered; another was recovering from multiple fractures and head injury when laparotomy became imperative. In this instance a torn mesentery was found with extensive hemorrhage. In these cases the mortality again depends on the number and severity of the injuries and the degree of trauma within the abdomen.

The diagnosis of intra-abdominal surgical pathology demands intensive observation for evidence of perforation and hemorrhage. The symptoms of shock and pain in various areas of the abdomen and lower chest with marked rigidity are important indications of torn bowel or mesentery.

The survival rate may be improved by early diagnosis and prompt surgery.

The author's experience is contrary to most reports, in that he observed a greater number of kidney injuries than injuries to the spleen; 42.5% had trauma to one or both kidneys in a group of 87 patients who had visceral injuries. Twenty-four percent of the kidney injuries resulted from Rugby football; thirty-one patients with renal injuries recovered and only two required nephrectomy, one of whom had pre-existing hydronephrosis and the other a fragmented kidney with thrombosed renal vessels. Three other patients with multiple visceral injuries in which the kidneys were involved died before operation could be attempted. It was considered that death was not attributable to the renal lesions.

Three patients with intraperitoneal rupture of the urinary bladder recovered after surgical repair. Two of the three with bladder ruptures were due to fractured pelvis. The third was due to a fall, the patient having a distended bladder.

There were 169 patients admitted with abdominal wall injuries and all of these were entered as possible intra-abdominal injuries. The severity of the injury varied greatly. Retroperitoneal hemorrhage produced symptoms similar to intraperitoneal lesions, with abdominal pain, shock, vomiting, absent bowel sounds and distension. Five patients with retroperitoneal hemorrhage were explored and two were found to have a rent in the peritoneum with blood draining into the peritoneal cavity.

The author concludes that a closed abdominal injury must be considered in all patients who have had a blow on the abdomen, especially if the patient presents abdominal pain and vomiting, tenderness, rebound tenderness, rigidity, and absent bowel signs. These are indicative of intraperitoneal or retroperitoneal lesion. Radiographic and intravenous pyelograms may be helpful.

The majority of single visceral injuries was 6%, while multiple visceral injuries produced a mortality of 46%.

Any surgeon who sees emergency abdominal injuries has undoubtedly had the same experience as the author. The ability to draw conclusions from the history and clinical findings is paramount, as it is extremely difficult to determine which patients demand immediate surgery. Intra-abdominal hemorrhage or perforation of a hollow viscus demands exploration. Injuries of the head, multiple severe fractures, added to intra-abdominal trauma, have to be evaluated as to which demands priority. In most instances fractures may be splinted temporarily and head injuries must await repair of perforations and control of massive hemorrhage.

During the years of my association with Dr. Farr, he demonstrated many times that the local anesthesia needle could be introduced through the abdominal wall without injury to the small intestine if there were no adhesions. On the strength of these demonstrations, I have repeatedly done peritoneal puncture for diagnosis. On some occasions I have ruled out hemorrhage in doubtful cases by a negative tap, or urine has been found when catheterization of the bladder revealed none. Intraperitoneal tapping with a needle is very rewarding and a harmless procedure. A resident who used this method for diagnosis phoned me in distress because he had inserted his needle close to an old laparotomy scar and obtained *gas. No harm resulted. I have repaired bladder rupture on several occasions and in one instance there were three or four pints of urine within the peritoneal cavity.*

Stanley R. Maxeiner, Sr., M.D.
Minneapolis, Minn.

David H. Wilson, M.D.: Research Assistant, Casualty Department of the General Infirmary at Leeds: Incidence, Aetiology, Diagnosis and Prognosis of Closed Abdominal Injuries, A Study of 265 Consecutive Cases.

EVALUATION OF PANCREATIC BIOPSY

A review of 159 pancreatic biopsy patients has been tabulated and evaluated. In six complications the pancreatic incision was considered the major factor, causing death by either leakage of pancreatic juice or pancreatitis. Three resulted from a Vim-Silverman needle, one from a wedge biopsy, and one from a combination of both techniques. There were nine nonfatal but serious complications. A needle placed anywhere in the pancreas has an excellent chance of entering the ductal system.

In terms of diagnostic value, the authors found that biopsy revealing chronic pancreatitis does not rule out carcinoma. The incidence of false negatives was about 35 percent. A biopsy is particularly dangerous in the obstructed pancreas.

Transduodenal needle biopsy of the pancreas obviates the damage or danger from pancreatic enzyme leakage, but does not eliminate the pancreatitis.

Biopsy is contraindicated in patients with unresectable lesions, and no specimen should be removed from patients with an obvious explanation for pancreatic masses, such as an associated duodenal ulcer. The authors do not biopsy the pancreas wherein the resectable lesion appears clinically to be carcinoma. They cite the experiences of Warren and Cattell who did pancreatic duodenectomies for benign disease in six of a series of 218 patients — with clinical judgment error of less than three percent.

In these pancreatic biopsies the complication rate was 9.5 and the mortality 3.8 percent, with accuracy of the pancreatic biopsy averaging 65 percent. The authors concluded that biopsy of the pancreas should be reserved for those resectable lesions which do not have the obvious features of neoplasm.

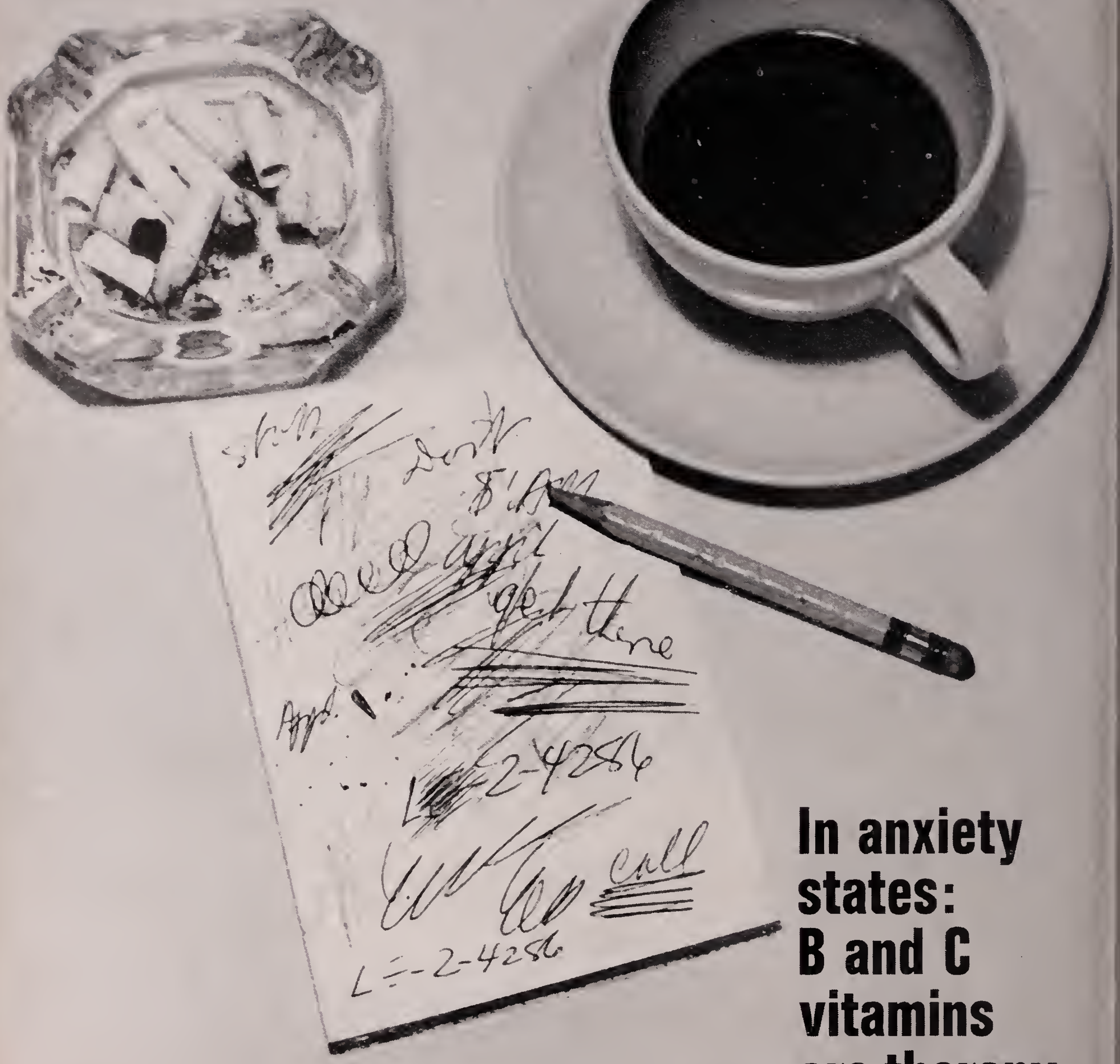
Any additional ammunition to aid the insistence upon clinical decision without benefit of biopsy is always of comfort to the surgeon who is willing to proceed with radical surgical management of the malignant pancreatic lesion.

J. H. Strickler, M.D.
Minneapolis, Minn.

Norman J. Schultz, M.D., Richard J. Sanders, M.D.: Ann Surg 158:1053, 1963.

Your Chances are Good

You have two chances — one of getting the germ and one of not. And if you get the germ you have two chances — one of getting the disease and one of not. And if you get the disease you have two chances — one of dying and one of not. And if you die — well, you still have two chances.—Author unidentified



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Book Reviews

A book is the only immortality.—R. Choate

INFECTIOUS DISEASES OF THE CONJUNCTIVA AND CORNEA — **Symposium of the New Orleans Academy of Ophthalmology. C. V. Mosby Co., St. Louis, 230 pages, price $12.50.**

This book represents the papers and round-table discussion of distinguished guests of the New Orleans Academy of Ophthalmology on the subject of infectious diseases of the conjunctiva and cornea. Although somewhat repetitious by its very nature it brings us a wealth of knowledge and experience with the "pink eye" in an informal, readable fashion. Primarily designed for the specialist, there are a number of points of interest to the general physicians as noted below.

Dr. Burns of Oregon Medical School states wryly that the most difficult task in selecting an antibiotic is to find one which is not mixed with a steroid. He discusses the mimeae which are organisms associated with antibiotic resistant gonorrheal urethritis. Dr. Givner of New York mentions a series of 258,621 babies receiving silver nitrate prophylaxis in which there were 17 cases of gonorrheal ophthalmia, concluding that no therapy invariably prevents this disease. Medicolegally, it is important not to call every oxidase positive gram-negative diplococcus infection gonorrheal without doing maltose fermentation, as meningococcal conjunctivitis is not rare. Dr. Allen of Boston describes how the cornea is not normally susceptible to the ubiquitous pseudomonas unless it is ulcerated, as occurs after removal of a foreign body, when polymixin-B containing drops should be used to prevent this severe infection. Dr. Kimura of San Francisco reiterates the sad sequelae of steroid-treated herpes simplex, changing what is normally a self-limited "cold sore" of the cornea into a blinding deep corneal infection often secondarily infected with fungi. Dr. Thygeson of San Francisco reviews the latest knowledge of trachoma which is an important cause of blindness outside this country. It is due to a large virus which is inhibited by certain antibiotics clinically. The deceased Dr. Gingrich of Texas reviews the increasing importance of fungus infections associated with the injudicious use of antibiotic-steroid medications.

William S. McClanahan, M.D.
Minneapolis, Minn.

ADVANCES IN THE TREATMENT OF MENSTRUAL DYSFUNCTION — **Alvin F. Goldfarb, Lea & Febiger Company, 188 pages**

This book is a collection of papers given by 14 well-known clinicians at a symposium held April 27, 1963, at Jefferson Medical College, Philadelphia, Pennsylvania.

These experts review the current knowledge available on several interesting topics. Included are reports on several new drugs including the pituitary stimulator Clomiphene®, and the many ovulatory inhibitors. This is not a standard textbook on menstrual disorders but acts as a specialized current supplement to them. It is recommended to all those practicing or interested in gynecologic endocrinology.

William N. Spellacy, M.D.
Minneapolis, Minnesota

SURGICAL PATHOLOGY — **Lauren V. Ackerman, 3rd Edition, C. V. Mosby Co., St. Louis 1964**

This enlarged and revised third edition is an aid and text welcome to all surgeons and pathologists who have found great usefulness in the previous editions since 1953.

For the clinician particularly, this text is an excellent companion piece to Dr. Ackerman's book, "Cancer."

The absence of color plates in a book of this type is very well compensated for by Dr. Ackerman's clear and concise descriptions which are amply supported by a great many photographs, some 1,216 figures in a total of 1,244 pages.

The orderly division of study by systems affords the student easy access to the material. The introductory chapter describes the value of various techniques of surgical pathology, and it should be carefully considered by all clinicians. The remainder of the book has long since become standard source or reference. Surgeons and pathologists must be grateful that Professor Ackerman has devoted his talent for writing and organization and his great scientific knowledge to our lasting benefit. The new third edition is an even better surgical pathology. It is certainly the outstanding book in this field.

J. H. Strickler, M.D.
Minneapolis, Minnesota

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Maternal Studies

Obstetric Infection Deaths in Minnesota*

Part I

ALEX BARNO, M.D.**
Minneapolis, Minnesota

This report is concerned with the analysis of the obstetric infection deaths from the Minnesota Maternal Mortality Study for the 12-year period, 1950 through 1961. A 10-year general summary has been published[1] and contains the bibliography regarding various aspects of the study.

Table 1 shows the Minnesota Maternal Mortality rates and preventability for the year 1941 (the study was done for a one-year period and discontinued then because of World War II) and for the 12-year period under consideration. This is self-explanatory and shows the tremendous progress made — the obstetric mortality rate is now down to 0.1 to 0.2 per 1,000 live births.

Obstetric and Nonobstetric Causes of Death

During the 12 years of the current study there were a total of 549 maternal deaths among 993,260 live births, 324 or 59% of which were classified as obstetrical and 225 or 41% nonobstetrical (Tables 2 & 3). Listed here are the primary causes of death as determined by the Minnesota Maternal Mortality Committee, even though in many instances there were several conditions which contributed to the patient's death. As can be seen in Table 2, infection is the second leading cause of death, surpassed only by hemorrhage. Whereas hemorrhage constitutes the greatest percentage of preventable deaths (46%), infection contributes only 10% of the total preventable deaths. To complete the picture, the nonobstetric causes of death are recorded in Table 3. The 12 peritonitis deaths in this group warrant brief mention. Six of these were due to intestinal obstruction; two were primary peritonitis (source undetermined); one was secondary to an unindicated cecostomy; one followed cholecystectomy; one was secondary to perforated carcinoma of the rectosigmoid colon, and one followed wound disruption after laparotomy for a pancreatic cyst.

Obstetric Infection Deaths, 1950-1961

Table 4 lists the categories included in the obstetric infection deaths. Sixty-five per cent, or two thirds, had post-mortem examination. *Pulmonary embolism* constituted the greatest percentage (41). Most maternal mortality studies list pulmonary embolism as a separate cause of death. The reasons for including this cause in the infection group will be discussed subsequently. *The septic abortions* constituted 30% of these deaths, *puerperal infections* 22% and *perforated appendicitis* 7%. It might be surprising to some that the Committee included the appendicitis deaths in the obstetric infection group. This is not under-correcting but in reality over-loading or over-indexing. Appendicitis in pregnancy is a "horse of a different color." The diagnosis is difficult because of pregnancy effect — nausea and vomiting, pressure pains or round ligament syndrome, changes in the anatomical position of the

Continued

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*Presented at John L. McKelvey 25th-Year Anniversary Celebration, Oct. 26, 1963.

**From the Minnesota Maternal Mortality Committee.

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appendix, loss of muscle tone in the multipara with spasm and rigidity less likely to be found, splinting by the gravid uterus and normal increase in the white blood count and sedimentation rate.

These four categories of the infection deaths will be discussed separately.

Pulmonary Embolism

Incidence

The incidence of pulmonary embolism is shown in Table 5. It should be stressed again that these diagnoses were those determined by the Committee and not obtained from data on the death certificates. The Committee discovered that during the first five years of the current study,[2] 25% of the death certificates were totally inaccurate as far as the cause of death was concerned. Most frequently listed cause of death (waste-basket, so to speak) was pulmonary embolism. For example, a patient died from post-partum hemorrhage; yet the death certificate cause of death was falsified as pulmonary embolism. The incidence of pulmonary embolism in the population as a whole varies according to age, frequency of surgery, and numerous other factors. It is known that one third of all postoperative deaths are due to pulmo-

TABLE 1
Minn. Maternal Mortality Rates and Preventability, 1941, 1950-1961

Year	Live Births	Total Mat. Deaths	Gross Mort. per 1,000 Live Births	Obstetric Deaths	Corrected Mort. Rate	Preventability No.	Preventability % of Total Mat. Deaths
1941	55,293	112	2.03	93	1.68	82	73
1950	76,074	68	0.89	47	0.62	22	32
1951	80,099	57	0.71	39	0.45	24	42
1952	78,990	58	0.73	31	0.39	10	17
1953	79,362	59	0.74	33	0.42	15	25
1954	81,033	40	0.49	27	0.33	12	30
1955	81,665	43	0.53	31	0.38	8	16
1956	82,620	45	0.54	26	0.31	10	22
1957	86,019	60	0.70	21	0.24	7	12
1958	85,594	26	0.33	14	0.16	3	12
1959	87,724	37	0.42	21	0.24	7	19
1960	88,126	29	0.33	17	0.19	6	21
1961	85,954	27	0.31	17	0.20	7	26

TABLE 2
Obstetric Causes of Death and Preventability, 1950-1961

Cause of Death	No.	%	Prev.	% of Total Prev. Deaths
Hemorrhage	93	29	58	46
Infection	54	17	14	10
Toxemia	52	16	21	17
Heart Disease	27	8	6	5
Amniotic Fluid Embolism	23	7	0	0
Anesthesia	16	5	11	9
Chorionepithelioma	14	4	0	0
Air Embolism	8	2	3	2
Others	37	12	13	10
Not determinable (11)	—	—	—	—
Transfusion deaths (6)	—	—	—	—
Dehydration and electrolyte imbalance (5)	—	—	—	—
Diabetes mellitus (5)	—	—	—	—
Idiopathic pulmonary edema (4)				
Suicide (post-partum psychosis) (3)	—	—	—	—
Pituitrin shock (2)	—	—	—	—
Unexplained shock (1)	—	—	—	—
TOTALS	324	100	126	99

nary embolism. It is also known from autopsy studies that in 50 to 65%, the source of the embolism cannot be found. In this series of pulmonary embolism deaths (22), an autopsy rate of 55% was obtained, and in only one third was the source of the embolism found.

Infectious Process

Some authorities feel that thrombophlebitis is an infectious process. The exact mechanism of thrombus formation is not known. Some authors, notably Ochsner, attempt to make much of differentiating thrombophlebitis from phlebothrombosis. This only creates a false sense of security in speculating as to the risk of embolism and is not justified. Both conditions are probably stages of the same process.

TABLE 3
Nonobstetric Causes of Death, 1950-1961

Cause	No.
Trauma	36
Malignant tumors	28
Poliomyelitis	25
Intracranial hemorrhage	23
Not determinable	19
Asian flu	16
Peritonitis	12
Leukemia	6
Infectious hepatitis	6
Pneumonia	6
Coronary occlusion	4
Glomerulonephritis	4
Lupus erythematosus	4
Panmyelophthisis	3
Pyelonephritis	2
Acute alcoholism	2
Ruptured aneurysm of splenic artery	2
Meningitis	2
Status asthmaticus	2
Spontaneous hemothorax	1
Insulin coma	1
Obstructed laryngotracheitis	1
Hereditary cystic disease of liver	1
Ruptured multiple pulmonary aneurysms	1
Hemorrhage from liver abscess	1
Acute rheumatic fever	1
Shock of undetermined origin	1
Bilateral spontaneous pneumothorax	1
Hypersplenism	1
Pulmonary tuberculosis	1
Obstruction of trachea	1
Thrombocytopenic purpura	1
Brain abscess	1
Status epilepticus	1
Spontaneous rupture of thoracic aorta	1
Dissecting aneurysm of aorta	1
Acute cerebral edema	1
Pulmonary aspiration of stomach contents	1
Tetanus	1
Cirrhosis of liver	1
Acute pulmonary edema	1
Infarction of GI tract	1
TOTAL	225

In this series of 22 patients, 11 or 50% had bona-fide pelvic infections and would have been included anyway. If one disagrees with the inclusion of pulmonary embolism in the infection category, the 11 patients with no evidence of infection can be omitted (some of them had clinical evidence of thrombophlebitis), leaving 43. If one still further disagrees about the inclusion of appendicitis, the other four can also be omitted, leaving 39 deaths in the infection category, still the third leading cause of death.

Predisposing Factors

The last large series regarding thromboembolic disease complicating pregnancy and the puerperium was published by Ullery[3] in

TABLE 4
Obstetric Infection Deaths, 1950-1961

Cause	No.	%
Pulmonary embolism	22	41
Septic Abortion	16	30
Self-induced or criminal (10)		
Spontaneous, incomplete (4)		
Nonindicated D & C (2)		
Puerperal infection	12	22
Perforated appendicitis	4	7
TOTAL	54	100

TABLE 5
Incidence of Pulmonary Embolism
1950-1961
22 deaths among 933,260 live births
.02 per 1000 live births
or
1 per 50,000 live births

TABLE 6
Predisposing Factors in 22 Pulmonary Embolism Deaths, 1950-1961

Factor	No.	%
Pregnancy	22	100
Operative procedure	14	64
Anesthesia	13	60
Anemia	12	55
Obesity	11	50
Infection	11	50
Varicose Veins	9	41

Continued

1954. He presented 172 patients with seven deaths at Philadelphia Lying-In Hospital, 1933-1953, and discussed the predisposing factors of thromboembolic disease. Table 6 is patterned after his list of predisposing factors. It is realized that data from 22 cases are not statistically significant. Pregnancy itself is a predisposing factor, since circulatory stasis is the most important pre-existing condition. The various factors listed in Table 6 are self-explanatory. With regard to the 13 anesthetics, 11 were general and two spinal.

Failure to Ambulate

Failure of early ambulation probably contributed to the development of pulmonary embolism in three instances. For example, one of these patients was a 200-pound, 18-year-old primigravida who had a midforceps rotation and extraction (ROP to OA) under spinal anesthesia after a 9½ hour second stage. She was kept at strict bed rest post-partum and expired on the 14th post-partum day from pulmonary embolism. This was proved at autopsy.

Deep Thrombophlebitis

Four of the 22 patients died undelivered. One of these was a 28-year-old para 1 with varicose veins of the lower extremities, who developed superficial thrombophlebitis of the right leg at 16 weeks gestation. She was treated at home with bed rest for 14 days, penicillin, heat and elevation. Response to the above therapy was excellent. At 29 weeks gestation she complained of pain and tenderness in the left groin. Examination revealed tenderness, redness, and localized edema involving the left saphenous vein over an area of two inches near the sapheno-femoral juncture. Diagnosis of superficial thrombophlebitis was made. The same therapy as previously mentioned was again instituted at home. She expired six days later (at 30 weeks gestation) from pulmonary embolism. With the findings in the sapheno-femoral juncture, one is highly suspicious that this patient had deep thrombophlebitis.

The over-all care of the patients expiring from pulmonary embolism was good. The Committee assessed the care in 17 as adequate and in only five as faulty and contributory to death. Only two of these 22 deaths were considered preventable. The protocol of one of these follows.

The patient was a 34-year-old para 2 who weighed 220 pounds. She consulted her physician at 12 weeks gestation because of superficial thrombophlebitis of the calf of the right leg (two areas about one inch in length, each involving varicosities). Physical examination was otherwise negative except for obesity. An elastic bandage was prescribed. At 13 weeks gestation she was admitted to the hospital because of sudden marked dyspnea. Positive physical findings were obesity, dyspnea, marked swelling of the entire right leg (described as twice the size of the left), and the two areas of previous superficial thrombophlebitis unchanged. Homan's test was not done. Diagnosis was probable pulmonary embolism. Treatment consisted of bed rest, oxygen and Aminophyllin. On the second hospital day her temperature was 99; her pulse rate remained rapid (112); and respirations were 20-28 per minute. On the third hospital day she was allowed bathroom privileges and was sent ambulatory to the doctor's office for X ray of the chest, since this was not available at the hospital. X ray of the chest was negative. An electrocardiogram was also obtained; there was no evidence of coronary disease, but the findings were consistent with pulmonary embolism. Her temperature was 99, her pulse rate 130, and she complained of pain in the calf of the right leg. Treatment consisted of Aminophyllin and Demerol, and the area of thrombophlebitis was painted daily with one-half strength iodine solution. Her condition remained the same for the next three days. The low-grade fever and rapid pulse persisted. On the seventh hospital day she complained of right chest pain. Demerol was prescribed. On the eighth hospital day she complained of severe pain in the chest and dyspnea, and she became cyanotic. Her temperature was 104°, and she developed shock. Heparin, 10 mg. every four hours was started. She remained in shock on the eighth and ninth hospital days. On the tenth day she aborted spontaneously at 8:15 a.m. There was no excessive bleeding. Because of the persistence of the shock, 500 cc. of whole blood were given. She then developed hemoptysis and expired at 10:25 a.m. Autopsy was refused, but the findings and clinical course were typical of pulmonary embolism. The two primary criticisms in the management of the patient were first, allowing her to be ambulatory; and second, the totally inadequate anticoagulant therapy.

To be continued next month

They say a baby is born every seven and a half seconds. And isn't it marvelous how we keep them so evenly spaced?—Changing Times

Perinatal Mortality Study

Venereal Disease

The mother in this case report was unwed, 24 years of age, and Rh positive. This was her first pregnancy. She had had no prenatal care. At 29 weeks of pregnancy she suffered premature rupture of the membranes and went into active labor. She denied any overt acts to initiate labor. The first stage lasted two hours and 45 minutes, with analgesia consisting of 1% Carbocaine infiltration of the perineum. Delivery was occiput anterior over an intact perineum. The second stage of labor lasted four minutes. The cervix was inspected — there were no tenaculum marks or presence of intervention. A culture was made of the cervix; no serologic test for syphilis was done.

The female infant weighed two pounds, one ounce and did not cry for five minutes. Apgar rating was 4. The infant's eyes were treated with silver nitrate and the upper respiratory tract was cleared of mucus. The infant was then placed in an incubator.

The day following delivery the laboratory reported the culture of Neisseria gonorrhoeae from the mother's cervix at delivery. She was treated with penicillin 1,200,000 units and the infant was given 25,000 units. The mother was discharged from the hospital three days following delivery. Repeat cervix cultures were not made.

The infant developed progressive respiratory difficulty, not alleviated by oxygen. A chest X ray at 48 hours of age revealed multiple miliary areas of atelectasis. The infant expired at 56 hours. Autopsy revealed bilateral severe atelectasis with no evidence of hyaline membranes and no evidence of gonorrhea or syphilis.

Comment

This case demonstrates the value of cervix cultures done at the time of delivery, particularly in unwed mothers. The Hennepin County Perinatal Mortality Study Committee feels that the presence of gonorrhea should be ruled out in every delivery. Furthermore, serologic test for syphilis, particularly in an unwed mother, should be made in every pregnancy. The dose of penicillin was sufficient for the gonorrhea but was less than half enough for the treatment of syphilis which may have also been present. The absence of serologic test for syphilis in the present case is a very serious error.

Physical ills are the taxes laid upon this wretched life; some are taxed higher, and some lower, but all pay something.—Lord Chesterfield

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Some people think that doctors and nurses can put scrambled eggs back into the shell.—Dorothy Canfield Fisher

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Special Article

Home Nursing Care in Steele County

An Experiment

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CHRISTINE LUND*
EMILY WHITE, PHN**
Owatonna, Minnesota

For many years, the Nursing Board of the Steele County Public Health Nursing Service has been aware of the need to provide more nursing services to the chronically-ill in the home. Often a patient can be discharged from the hospital if the family is able to continue his care at home. Before he leaves the hospital, however, he or his family are taught exercises and some procedures such as giving insulin, applying dressings, crutch-walking, et cetera. Sometimes family members are so worried about their ability to care for the patient that they do not even hear all of the instructions and need a repetition. It may be questioned whether a patient should remain in the hospital, go to a nursing home, or be allowed to go home. The nursing board realizes that patients are happiest in their familiar surroundings.

The Steele County Nursing Board is composed of citizens in our community who are interested in guiding, assisting and interpreting our public health nursing program. In addition to volunteer representatives of the various communities, the Board must legally include a physician, a county commissioner, and the county superintendent of schools.

A Home Nursing Care Experiment

This summer the Steele County Public Health Nursing Service had the opportunity of participating in the Minnesota Department of Health Nursing Assistant Program. Five students in collegiate schools of nursing who have completed their junior year were employed as nursing assistants for the summer school vacation months by the Department of Health.

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*St. Olaf College, School of Nursing.
**Steele County Public Health Nursing Service.

Home Visits

The nursing assistant visited 17 families at least once a week, and sometimes three and four times. A total of 240 visits were made to the 16 patients. Two hundred and five visits were to patients 65 years old and over, and 35 to patients under 19 years of age with chronic illness.

Services Performed

The public health nurse made the initial visits to these families and continued supervision of their care. On a selected basis some were transferred to the nursing assistant who functioned as a practical nurse. During her visits she performed physical treatments such as changing dressings for one patient, giving injections for two patients, giving enemas for two patients, assisting six patients with bed baths or tub baths, and washing hair for two patients. In three different instances, a reddened area which could have developed into a decubitus was found. By instructing the family member or home nurse aide how to massage the area and relieve the pressure, the decubitus was prevented. The nursing assistant taught the patient and his family how to prevent muscle contractures by demonstrating good body alignment. She taught the family how to do range of motion exercises; in some instances, she herself did the exercises for the family.

Benefit Derived

These exercises helped the patient to develop more extensive range of motion and to improve his muscle tone. The nurse further aided the patient and his family in regaining incentive. By contacting and co-ordinating the efforts of family and friends, she was able to assist five patients to go outdoors after one to several months inside the house. After exercises, teaching mobilization activities, and much encouragement, five of her patients began to walk or improve their walking during the summer.

Case History

Hip Fracture

A patient with a fractured hip had been taught how to walk and to do exercises. He had purchased a walker to facilitate mobilization, but because of his fear of falling when he was alone in his apartment, he had not followed medical recommendations and had resorted to his wheelchair. This patient requested the nursing assistant to help him with his weekly bath, an activity approved by his physician. After many weeks, the patient began talking about learning to walk and showed interest in going outside. The doctor, nurse, and physical therapist initiated a rehabilitation program. The patient's confidence in himself took time to develop, but with encouragement and instruction from his doctor, and with consistent help from the nurse, he is learning to walk and is making weekly excursions outside. He is happy with the prospects of his future independence.

Acute Infection

A woman felt that she must do everything for her husband who had just suffered an acute infection during his rehabilitation. She fed him, dressed and undressed him, and hovered nervously as he was transferred from the bed to the commode. Soon he too felt that he was helpless and worthless; he did not feel strong enough to sit up for more than a half hour a day. Semiweekly visits from the nurse helped his wife to understand the value of allowing him to do as many activities for himself as his doctor felt he was able to do. The nurse used a slow, relaxed approach as she demonstrated several ways in which he could help himself. She praised his wife when she finally was able to step aside and watch him struggle for 10 or 15 minutes to put on his bathrobe, to raise himself to a sitting position on the edge of the bed, and to eat by himself. Now he is showing more interest in doing many other things for himself.

Metastatic Cancer

A woman with metastatic cancer was rapidly becoming more debilitated. Her daughter and husband were caring for her in the home. As she became weaker, her care was becoming more difficult for her daughter. Neither the patient nor the members of her family wanted to admit that she was going to die soon. The nursing assistant visited the home three times a week to help with the physical care and to give emotional support to the patient and her family. At first she did range of motion exercises and helped to transfer the lady to a chair. The nurse assisted the daughter in turning and moving her mother. Occasionally, she gave an enema or a bed bath to allow the daughter to have time away from home. As the patient became progressively weaker, the nurse was able to talk with both the husband and the daughter privately about the approaching death. They were able to express their feelings to her, and eventually to accept the reality of this coming event and to prepare themselves for it. After the patient died, the nurse visited the family a few times. They appreciated having someone to whom they could express their feelings and their adjustments to living without the patient. They both seemed very proud that they had been able to care for the mother and wife until she died.

Cardiac Disease and Arthritis

A lady with arthritis and cardiac disease had almost given up hope for improving and was regress-ing. She was a bed patient with no control of her bowel or bladder. Under the physician's guidance the public health nurse was able to encourage this lady to control her bowel and bladder, to sit on the edge of the bed, to transfer to a wheelchair, and to care for herself partially. When this lady heard about the nursing assistant program, she decided she would like a weekly tub bath. About two weeks later she asked to have her hair washed. During her midsummer report to the doctor, the nursing assistant discussed ambulation for this patient. Soon she was walking on her crutches to the supper table each night.

The Team Approach

Under the direction of the doctor, other members of the health team are often beneficial in working toward achieving optimal health for the patient. The physical therapist, the home nurse's aide, the hospital nurse, the family members, the practical nurse, the professional nurse, and the patient comprise the team of which the doctor is the head. The public health nurse first evaluates the total home situation and decides what member of the nursing team can best meet the nursing needs of the patient. Her understanding of the home environment, the physical home construction with possible hazards, interpersonal relationships in the family: these can be informative to the doctor in his own evaluation of the patient's home situation. The nursing assistant can perform, demonstrate, and teach nursing procedures. When she is not prepared to do this, the public health nurse takes the responsibility. The assistant has time to listen for an hour or so while the patient, his family, or the home nurse's aide uses her as a "sounding board." They may enjoy reminiscing about past pleasant memories or they may appreciate having an "outsider" to talk with about their plans, their hopes, their accomplishments, and their worries.

Obviously communication between team members is essential. After the first visit and periodically during the patient's rehabilitation, the nurse reports to the doctor concerning the patient's progress and home situation.

Summary

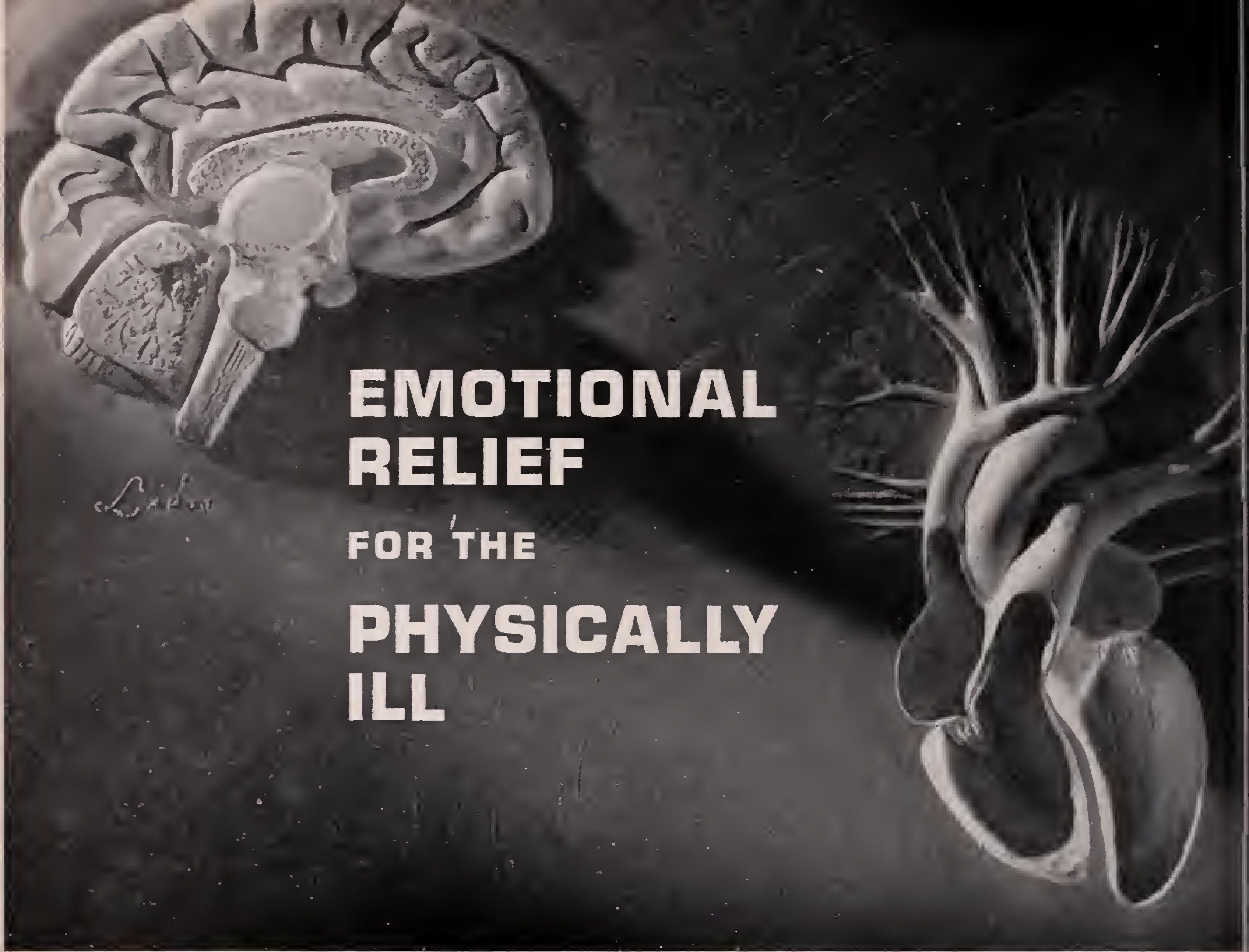
Through this encounter with concentrated home nursing care, it is hoped that other nursing boards will be provided with ideas for similar programs. We feel that our nursing assistant was working to capacity with an average of twenty home visits per week. With decrease in frequency of visits due to patients' increased independence, deaths, and changes of residence, the case load varies. Taking all these factors into consideration, we estimate that a nursing assistant could give service to approximately 50 or 60 patients per year.

One area that needs further exploration is the most efficient method for the physician to make his referral to the nursing service and to continue communication. We would prefer to have patients who are in need of physical care or emotional support referred directly by the physician. Through this experience, the nurses have experimented with more thorough, accurate, and frequent means of communication with doctors.

In addition to our home care examples, the value of this type of bedside care can be summarized in three fields: rehabilitation, confidence, and teaching. Progress in rehabilitation seems to be greater and more consistent due to the constant encouragement and sincere interest from the nurse. The patient's confidence in himself and his own ability seems to have an increased chance to be established. With concentrated nursing visits, teaching can be on a gradual step-by-step basis.

There are many variables which cause a patient to progress or to regress: the nature and the extent of the disease, the patient's personality, the encouragement and support from family members, the availability and effectiveness of professional guidance.

In conclusion, it is evident that an additional person in the public health nursing service, whose role is to give concentrated home nursing care to the chronically ill, could contribute something to these patients that no other discipline can provide. It is also apparent that the need for medical direction and team effort in the public health nursing service is essential in establishing effective nursing care that will "egg on" the patients toward independence and health.



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History of Medicine

Benjamin Rush

1745-1813

During the formative period of our country, when we were emerging as a nation from the dominion of the English colonial system, Benjamin Rush, physician, patriot, and signer of the Declaration of Independence, altho both praised and condemned, comes forth as the first great physician of the United States of America. Receiving his education at Princeton and Edinburgh, be began his career in 1769 as professor of chemistry in the College of Philadelphia, which merged into the University of Pennsylvania in 1791. There he attained the chair of institutes of medicine. He was also physician to the Pennsylvania Hospital (1783-1813), the chief founder of the first Dispensary in this country in Philadelphia in 1786, and Treasurer of the United States Mint (1799-1813).

Doctor Rush's great moral courage and physical stamina was put to a severe test during the yellow fever epidemic of 1793. When Philadelphia was in a complete state of chaos and thousands dying, he endangered his own health by treating 100 to 150 patients a day. Altho stricken with the fever twice, he was completely fearless in exposing himself, "During the tragic epidemics of yellow fever, according to Powell, 'There was only one doctor who would enter a fetid chamber, scorn all protections, sit on the edge of a vomit-soiled bed, smile cheerfully to the frightened patient, say blandly, "you have nothing but a yellow fever" ' "[1] He never did arrive at the real cause of the epidemic, the aegypti, brought in by ships to the waterfront district, but he, ahead of his time, urged that the city clean up the streets and drain the ponds, complaining about the swarms of mosquitoes. "His scheme of treatment was the exhibition of large doses of calomel and jalap, copious blood-letting, low diet, low temperature in the sick-room, and abundant hydrotherapy, within and without. As a blood-letter, Rush has been likened to Sangrado, but he saved many patients and, when sick, as he thought, of yellow fever, consistently submitted to his own line of treatment."[2] "Rush bled and purged without mercy . . . the majority of the physicians followed his precepts . . . and every apothecary in town overworked himself to fulfil his calomel-and-jalop prescriptions. . . ."[3]

In the midst of both criticism and praise, Rush became a prolific writer. His dictatorial, altho incorrect assertions about various diseases and their treatment, show the strong-willed cocksure individual that he was; "Rush knew less about diabetes than Aretaeus, and less about pulmonary consumption than Galen. He declared the latter disease was not contagious, and he invariably prescribed exercise for the consumptive: as for the treatment, he gives us the specific: 'The pulmonary consumption . . . even when tending rapidly to its last stages has been cured by bleedings, digitalis and mercurial salivation.' In fact, this heroic doctor did not fear any disease; concerning scarlatina, he wrote: 'Whenever I have been called to a patient where the scarlatina appeared to be in a forming state, a vomit of ipecacuanha or tartar emetic, mixed with a few grains of calomel, has

Continued

never failed of completely checking the disease. . . . When the matter which produces this disease has been received into the body, a purge has prevented its being excited into action, or rendered it mild, throughout a whole family.' Even lock-jaw held no terrors for him; 'Tetanus is prevented by inflaming the injured parts . . . and often cured by opium, bark and wine.' He admitted hydrophobia was a formidable disease, but he added that he could prevent the manifestations by giving mercury, and cure the malady itself by copious bloodletting."[4]

That the strong-headed Doctor Rush took himself very seriously is evidenced by the often-quoted remark of Oliver Wendell Holmes. "In reply to Rush's pompus epigram, 'Medicine is my wife and Science is my mistress' Holmes answered: 'I do not think that the breach of the seventh commandment can be shown to have been of advantage to the legitimate owner of his affections.' "[5]

Doctor Rush was a pioneer in psychiatry, considered by many to be its Patron Saint. Altho his "tranquilising chair" was a gruesome contraption, he gained considerable insight into the treatment of mental illness. In his book, MEDICAL INQUIRIES AND OBSERVATIONS UPON THE DISEASES OF THE MIND, he propounds the theory that "buried memories" have an influence on current illness. To quote from the fifth edition, published in 1835; "Many diseases take place in the body from causes that are forgotten, or from sympathies with parts of the body that are supposed to be in a healthy state. In like manner, depression of mind may be induced by causes that are forgotten; or by the presence of objects which revive the sensation of distress with which it was at one time associated, but without reviving the cause of it in the memory. . . ." Eighty years later this conjecture of "original causes" that had "perished in the memory" was renewed by Breuer, and later by Freud.

"In the latter part of his life, after having married a wife (from the prominent Stockton family of New Jersey) and begot thirteen children by her, he writes in treating the causes of insanity, 'celibacy is pleasant breakfast, a tolerable dinner, but a very bad supper. The supper is not only bad, but eaten alone, no wonder it sometimes becomes a predisposing cause to madness.' "[6]

"Rush was our pioneer prohibitionist, and his 'INQUIRY INTO THE EFFECTS OF ARDENT SPIRITS' went into several editions; Rush who had a flair for publicity, himself sent a thousand copies to the Presbyterian Church for distribution. Its scientific value may be judged from this typical passage; 'A noted drunkard was once followed by a favorite goat, to a tavern, into which he was invited by his master, and drenched with some of his liquor. The poor animal staggered home with his master, a good deal intoxicated. The next day he followed him to his accustomed tavern. When the goat came to the door, he paused: his master made signs to him to follow him into the house. The goat stood still. An attempt was made to thrust him into the tavern. He resisted, as if struck with the recollection of what he suffered from being intoxicated the night before. His master was so much affected by a sense of shame, in observing the conduct of his goat to be so much more rational than his own, that he ceased from that time to drink spirituous liquors."[7] Doctor Rush was so active in the anti-alcoholic crusade movement that the W.C.T.U. later erected a commemorative tablet in front of his tomb in Christ Church Cemetery in Philadelphia.

His inquiring mind led him into many fields. He wrote the first American textbook on chemistry . . . was a founder of the American Anti-Slavery Society . . . active in promoting the establishment of public schools . . . worked for prison reform . . . influenced Thomas Paine to write "Common Sense" . . . was one of the founders of the College of Physicians, and an influential member of the American Philosophical Society. Doctor Rush stands out especially in his services to medical teaching, in helping to prepare American physicians for our rapidly expanding country.

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Bad Temper

As a youngster I once happened to see a man opening a door in a hurry, and when things did not go as he wished, he bit the lock, kicked the door, and reviled the gods; his eyes became wild like those of a madman, and he almost foamed at the mouth like a boar. At this I took such a hatred against temper as to wish never to be seen disgracing myself in one.

Restrain and hide your anger within yourself. For though one cannot become void of anger by the mere wish, one can control the unseemly manifestations of this passion. — Galen

---

For Diseases of the Fundament

For diseases of the fundament, a sovereign remedy is bear's gall, mixed with the grease; to which some persons are in the habit of adding litharge and frankincense. Butter, too, is very good, employed with goose-grease and oil of roses. Bull's gall upon lint is a remarkably useful remedy, and has the effect of making chaps of the fundament cicatrize with great rapidity. Bear's blood is curative of inflamed tumours and apostemes upon these parts in general; as also bull's blood, dried and powdered. The best remedy, however, is considered to be the stone which the wild ass voids with his urine, it is said, at the moment he is killed. This stone, which is in a somewhat liquefied state at first, becomes solid when it reaches the ground: attached to the thigh, it disperses all collections of humours and all kinds of suppurations: it is but rarely found, however, and it is not every wild ass that produces it, but as a remedy it is held in high esteem.

— Pliny

See Minnesota Medicine, June 1964, Page 716.

A pioneer is a person whose annual property tax now exceeds what he paid for the place to begin with.—Changing Times

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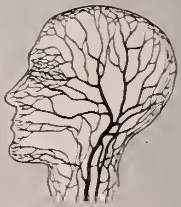

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Meetings and Announcements

The joy of meeting, not unmixed with pain.—Longfellow

AUGUST

American Academy of Physical Medicine and Rehabilitation, Statler-Hilton Hotel, Boston, Aug. 24. Pres.: Morton Hoberman, M.D., 5900 Arlington Ave., Riverdale 71, N. Y.

American Association of Blood Banks, Shoreham Hotel, Washington, D. C., Aug. 25-28. Info.: Lois J. James, 30 N. Michigan, Chicago 2.

American College of Surgeons (Montana chapter), East Glacier, Mont., Aug. 22. Sec-Treas.: W. H. Randall, M.D., Miles City Clinic, Miles City, Mont.

American Congress of Physical Medicine and Rehabilitation, Statler-Hilton Hotel, Boston, Aug. 23-28. Exec. Dir.: Glenn Gullickson, Jr., M.D., 30 N. Michigan, Chicago.

American Hospital Association, Palmer House, Chicago, Aug. 24-27. Dir.: Edwin L. Crosby, M.D., 840 N. Lake Shore Dr., Chicago 11.

American Institute of Ultrasonics in Medicine, Statler-Hilton Hotel, Boston, Aug. 22. Sec-Treas.: Edwin Matlin, M.D., 220 Stewart Ave., Garden City, N. Y.

American Society of Pharmacology and Experimental Therapeutics, Inc., University of Kansas, Lawrence, Kan., Aug. 23-27. Sec.: Sidney Udenfriend, 9650 Wisconsin Ave., Washington 14, D. C.

American Society of Human Genetics, Boulder, Colo., Aug. 22-28. Sec.: Samuel H. Boyer, M.D., Johns Hopkins Hospital, Baltimore 5.

International Conference on Preventive Cardiology, University of Vermont, Burlington, Vt., Aug. 24-28. Info.: W. Raab, M.D., 206 Summit St., Burlington, Vt., 05401.

Rocky Mountain Radiological Society, Brown Palace Hotel, Denver, Aug. 20-22. Sec-Treas.: John H. Freed, M.D., 4200 E. Ninth Ave., Denver 20.

West Virginia State Medical Association, Greenbrier Hotel, White Sulphur Springs, Aug. 20-22. Exec. Sec: William H. Lively, Box 1031, Charleston, W. Va. 25324.

Wyoming State Medical Society, Jackson Lake Lodge, Moran, Aug. 31-Sept. 3. Exec. Sec.: Arthur R. Abbey, Box 2266, 4020 House Ave., Cheyenne.

SEPTEMBER

American Association of Medical Clinics, Americana Hotel, Bal Harbour, Fla., Sept. 16-18. Sec.: R. S. Condie, M.D., Palo Alto Medical Clinic, 300 Homer Ave., Palo Alto, Calif.

American Association of Obstetrics and Gynecology (members and invited guests), Homestead, Hot Springs, Va., Sept 10-12. Sec.: Clayton T. Beecham, M.D., 3911 Vaux St., Philadelphia 29.

American College of Obstetrics and Gynecology (District 2), Concord Hotel, Lake Kiamesha, N. Y., Sept. 24-27. Exec. Dir.: Donald F. Richardson, 79 W. Monroe, Chicago 3.

Southern Minnesota Medical Association annual meeting, Thursday, September 10 in Mankato, Minnesota. Contact: John J. Eustermann, Mankato Clinic, Mankato, Minnesota.

Minnesota Heart Association and Mayo Clinic Symposium on Clinical Applications of Electronics in Cardiovascular Disease, September 10 and 11, Rochester. Contact: J. F. McCally, Secretary, Mayo Clinic, Rochester.

Minnesota Academy of General Practitioners Fall Refresher Course, September 15-17, Leamington Hotel. Contact: W. H. A. Watson, M.D., Midway Medical Building; St. Paul.

Twin Cities Diabetes Association and Methodist Hospital Annual Symposium "Current Management of Diabetes Mellitus" September 19th at Methodist Hospital. Contact: Donnell D. Etzwiler, M.D.; St. Louis Park Medical Center; 4959 Excelsior Blvd., Minneapolis, Minnesota.

ANNOUNCEMENTS

Next scheduled Part I (written) examination of American Board of Obstetrics and Gynecology, will be held December 11 at 2:00 P.M. at various examining centers. Candidates eligible to take test will be notified on or about November. Contact: Clyde L. Randall, M.D.; 100 Meadow Road, Buffalo, New York.

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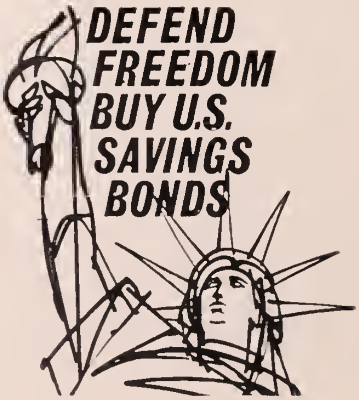

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Medical Economics

Guides for Reviewing Health Insurance Listed

Rising costs of medical care may weaken your patient's health insurance protection unless policies are kept up to date.

Physicians can perform an important service to their patients by explaining to them what factors should be considered when planning or updating health insurance for an individual or a family.

Here are some guides for reviewing health insurance prepared by the Health Insurance Institute. These suggestions could be helpful to you in advising your patients and incidentally, updating your own coverage.

You should check the details of your coverage at least every two years to make sure it fits the needs of a changing family, that it's keeping pace with costs and does not contain wasteful duplication.

The first step is to read your policies or certificates of coverage and jot down anything you don't understand in them.

Then take these points up with a specialist — your insurance representative for family and individual policies or your company or union welfare officer for group policies.

Date Provides Clue

The date on your policy will provide a clue as to its ability to cover present day costs.

Was it written in 1957? Hospital room and board costs have gone up 51 per cent since then because of higher labor costs and improved techniques and services. On the other hand, the cost of prescriptions has dropped slightly. Your coverage should take these relationships into account.

How about your disability income policy? If it was written to fit your $4,000 salary in 1954 it will hardly be sufficient protection if you are earning $8,000 in 1964.

More than 70 per cent of the health insurance coverage in effect today is through employer-employee group policies. A group plan can serve as an excellent base to add individual or family coverage.

Perhaps you have only basic hospital-surgical expense insurance through your employer. You should consider an individual or family major medical expense policy that would supplement it by providing protection against the catastrophic costs of a long and serious illness.

Program Disability Benefits

If your employer allows a certain amount of sick leave, you might consider acquiring a disability income policy that would provide weekly or monthly benefits after sick leave runs out in a long illness.

You also should examine your policies closely for duplicate coverage — two or more policies which cover the same class of medical expense. The Health Insurance Council

Continued

estimates that about 13 per cent of those with health insurance have duplicate coverage.

Such a situation could come about, for example, if you had an individual hospital expense policy and then went to work for an employer who provided group hospital expense protection.

Eliminate such overlapping coverage by diverting some of your premium dollars into unprotected areas, such as major medical expense.

Examine Efficiency

Take a close look at the overall efficiency of your insurance, too. So-called "first dollar" coverage that pays small claims is relatively more expensive than major medical coverage that eliminates the small claims through a deductible but provides protection against catastrophic bills.

Each family should have a provision in its budget for routine medical bills that will not be covered by insurance benefits.

President's Letter continued from Page 907

Providing a staff for emergency departments is a problem which must be faced by physicians. The holder of a license to practice medicine is the only one who can practice medicine so the local physicians are responsible for determining the best plan for their community and also for attempting to get the population to go along with it.

Concern about the future of hospitals has led to voluntary efforts at areawide planning so as to develop proper facilities and services. To be effective this "voluntary" planning must be supported by the financial agencies of the area. Leaders of planning movements maintain that even physicians' offices should be located in community health centers, as part of a formally organized regional system of facilities and services. There are advantages and disadvantages to the location of doctors' offices in or adjacent to hospitals. The American Public Health Association believes that regional planning constitutes the correct approach to health care with the community health service center as the key structure.

The House of Delegates of the American Medical Association considered planning activities at the 1962 clinical meeting and urged medical societies and individual physicians "to demonstrate cooperation and exert leadership in the formulation and operation of these regional planning bodies and be alerted to fight enabling legislation that would convert this from a voluntary to a compulsory system."

The final answer to the whole problem is surely not clear. I hope this reporting of one phase of Physician-Hospital relations will stimulate interest in the entire matter.

J. P. Medelman M.D.

J. P. Medelman, M.D.
President
Minnesota State Medical Association

Epilepsy

Many famous people have been victims of epilepsy — Van Gogh, de Maupassant, Leonardo da Vinci, Napoleon, Alfred Nobel, Saint Paul, Pascal, Handel and others. To dispel the superstition that surrounds epilepsy, The Epilepsy Foundation is sponsoring Epilepsy Information Month during August. Further facts are available by writing to The Epilepsy Foundation, Washington, D. C. 20005.

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COVER PHOTO:
Mayo Brothers Statue in Mayo Park, Rochester, Minnesota

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Bibliographical references should be limited to twelve and should be typed in conformity to the method used by the Index Medicus. They should be numbered consecutively in the order in which they first appear in the text. Book references should give the name of the author, title, edition number, publisher, and the year.

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LEDERLE LABORATORIES, A Division of AMERICAN CYANAMID COMPANY, Pearl River, New York
Lederle
7516-3

President's Letter

The listlessness of the summer doldrums is upon us as this is being written. The title of this page becomes gratifying. It lets me off the hook. A letter is a written communication according to my book. If a timely and pertinent cause in the messianic sense presents itself when a letter is being written, so much the better. If no such cause is at hand, one can still communicate — particularly if there is a deadline that must be met as in this case.

Occasionally, serendipity enters the picture. It did in regard to my August letter which concerned physician relationships to area-wide hospital planning. That was written well in advance of the hassle that goes on among three groups, each seeking a hospital monopoly not far north of the Twin Cities. Each group feels that by divine right it has the sole privilege of constructing and operating the facility. Surely they cannot all be correct in their assumptions. I hope the problem will be legally and morally solved by the time this appears in print. I hope even more that physicians will have played their proper part in the settlement. Hospitals, regardless of how many millions of dollars go into bricks and mortar, but without whole-hearted physician support, could be pretty empty symbols of power and gamesmanship. And empty, not only figuratively.

The annual meetings of your State and National Associations are over. I tried to convey my main impressions of our Minnesota State Medical Association meeting in the July issue of this Journal. I realize that I shouldn't say this, but I thought that the American Medical Association meeting was not very exciting. If there were earth-shaking developments I failed to recognize them, though foundations were laid for such developments. The July 6th AMA Medical News gives details on major actions.

Federal medicare pressure was temporarily off — no sweat at the moment. The San Francisco newspapers, to keep up circulation, had to fall back principally on reporting House of Delegates resolutions on smoking and human rights. I am sure that many members of the AMA are dissatisfied with the resolutions and for opposite reasons. Some consider them too weak and some consider them too strong. However, I do believe that the House of Delegates usually comes up with the correct answer. History confirms this belief.

Of special interest to Minnesota physicians was the election of our neighbor, Dr. Donovan F. Ward of Dubuque, Iowa, to the office of President-Elect of the Association. Many of us know Dr. Ward and have great confidence in him because we recognize his ability. His elevation to his high office is also gratifying because it again disproves the conviction of so many Association members that medical politics are cut and dried, power-packed and machine-run. The history of Dr. Annis, immediate Past-President in AMA affairs, further confirms this observation.

I thought that the Scientific Sessions were

Continued on Page 1128

thrown
for
a loss...

Keeping flies out of pharmaceutical production areas is important, yet entrances must accommodate heavy traffic of people and materials. In fact, at Eli Lilly and Company, the entrances to certain production facilities where traffic is heaviest have no screens or doors. □ This makes it look easy for flies to get in. But let one try it and he is literally picked up by a fast-moving blast of air and thrown for a loss—back outside. This "curtain of air," moving down and out from the top of the open doorway, bars the entrance and keeps flies out . . . still another step demonstrating the care that goes into the finished product.

Eli Lilly and Company • Indianapolis 6, Indiana, U.S.A.

Lilly

401004

Pulmonary Mycosis

Diagnosis
Of

CORRIN H. HODGSON, M.D.*
LYLE A. WEED, M.D.**
Rochester, Minnesota

ALTHOUGH RECOGNIZED instances of pulmonary mycosis are not common, the very possibility of its occurrence requires consideration in many cases of simple as well as obscure conditions involving the lungs. Many persons are infected with some of the mycoses, such as histoplasmosis and coccidioidomycosis, manifested by a positive result on a skin test or by fibrosis or calcification of the lungs. Yet, because of their benign, self-limited nature, few of these infections come to the attention of the clinician. Others, however, follow a progressive course — even causing death, which makes clear the importance of this minority group of pulmonary invaders.

Many comprehensive reviews are available to the physician interested in this problem, and no attempt will be made here to deal with the specific diseases individually. Rather, this article will be limited to the general problems of when to consider the mycoses as diagnostic possibilities and how to investigate for them.

Although most pulmonary mycoses come to attention because roentgenography of the chest reveals a lesion, there is no roentgenographic characteristic that points to mycotic

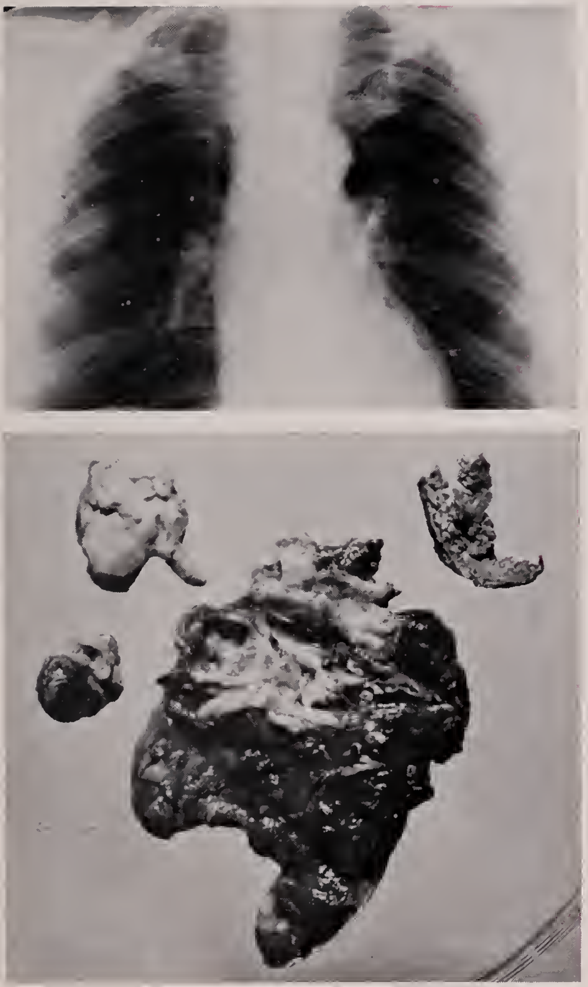

Fig. 1 — Solid-appearing lesion which actually was thin-walled cyst filled with matted filaments of aspergillus organisms.

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**Section of Microbiology, Mayo Clinic and Mayo Foundation.

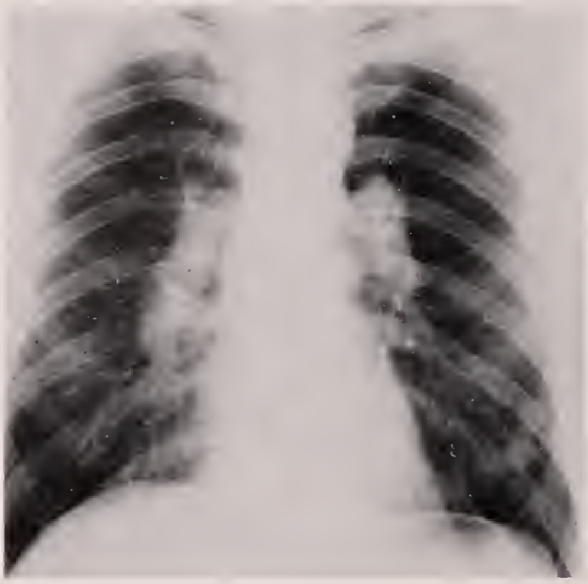

Fig. 2 — Peripheral granuloma due to cryptococcal infection in left lung. Bilateral hilar adenopathy due to cryptococcosis or sarcoid.

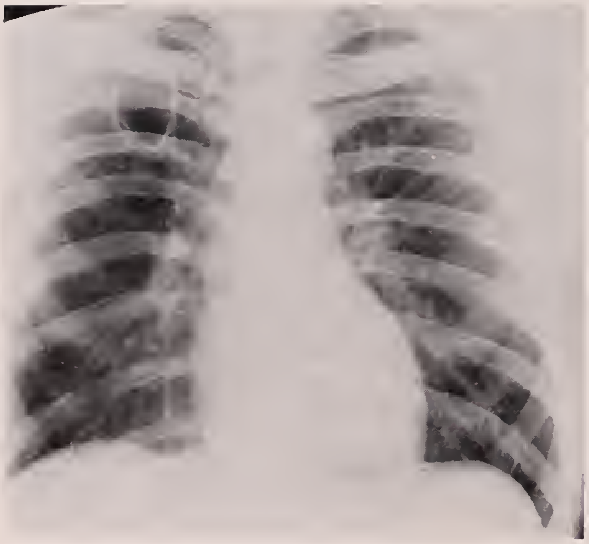

Fig. 3 — Thin-walled cavity typical of coccidioidomycosis.

infection rather than some other pulmonary disease. The involvement varies from solitary and nodular to extensive and bilateral, and cavitation is a frequent feature (Fig. 1-5). Resemblances are found with diffuse fibrosis, pulmonary edema, tuberculosis (miliary, exudative, or fibrous), primary or metastatic tumors, or pneumonia. The healed lesion may leave a residue of diffuse miliary or scattered calcification, a Ghon complex, or fibrosis and contraction of part of the lung.

Nor does the clinical pattern indicate anything more specific than just a disorder of the lung. Fungous infections ordinarily are chronic, occasionally fulminating. The usual bronchopulmonary symptoms and physical findings are to be expected, but are not characteristic of mycosis.

Without clinical or roentgenologic means to make a diagnosis, one is left with three laboratory methods: (1) immunologic, (2) histologic, and (3) microbiologic. Only recognition of the organism can make a diagnosis definite, but other important laboratory information may be corroborative. The clinician must bear the burden of evaluating the laboratory findings as applied to his patient, and this is not always easy. Therefore he must recognize the limitations of both a positive and a negative result, must apply the findings to the case in question, and must decide whether to defer diagnosis, to proceed with the information at hand, or to request more investigation.

Therapy, both medical and surgical, is now available for some of the myocoses. But it is not the same for all, and therefore recognition of the offending organism is imperative, so that therapy specific for that organism can be instituted.

Immunologic Investigation

Serologic Tests

Complement-fixation and precipitin reactions are available for investigation of some of the fungous infections. They provide useful corroborative information but unfortunately are not diagnostic. They are somewhat lacking in practical value to the physician because of cross reactions with other diseases, negative results or low titers sometimes found in the presence of a fungous disease, the need for serial tests over a considerable period to be significant, the difficulty of interpreting results, and the scarcity of facilities for performing the tests. One need not feel remiss in not having these procedures available, but they are of interest to the investigator.

Skin Tests

Skin tests are performed with fungous antigens and are applied and interpreted in the same manner as the tuberculin test. They should be read after 48 hours. An induration of 5 mm. or more is considered a positive reaction.

Antigenic material is available for blastomycosis, histoplasmosis, and coccidioidomycosis. We have discontinued using the blastomycin skin test because it was found to be valueless. Only about one fourth of our patients with proved blastomycosis reacted to the antigen. Of our patients with histoplasmosis and coccidioidomycosis, about half reacted — a rather low figure. Clearly, the skin tests are of little help in confirming or ruling out a diagnosis of histoplasmosis or coccidioidomycosis in an individual patient, although they may be helpful to the epidemiologist. It is well known that results of these tests may remain negative for some time after infection and also may revert to a state of anergy when the disease is progressive or terminal. It is hoped that the improved technics for preparing antigens may give reliable results of diagnostic value.

Histologic Investigation

Tissue to be examined for fungi may be obtained by incisional or needle biopsy or by surgical resection. The specimen is divided when obtained, one part going to the pathologist and the other to the microbiologist.

Nonspecific Granuloma

Histologically the fungi produce a granulomatous reaction consisting of focal proliferation of histiocytes with or without caseation and usually associated with giant-cell formation. There is no tissue reaction

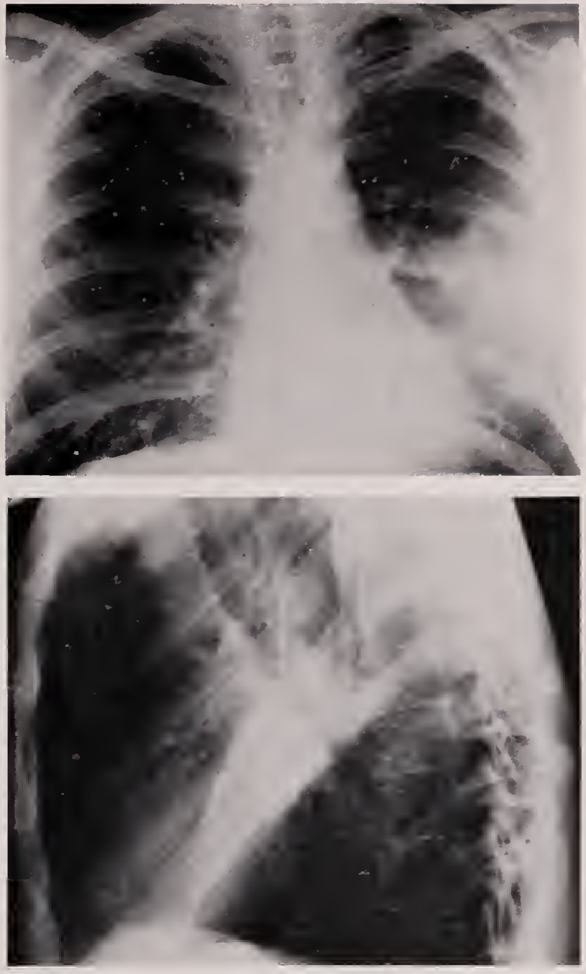

Fig. 4 — Pneumonitis of the left upper lobe including lingula, due to blastomycosis.

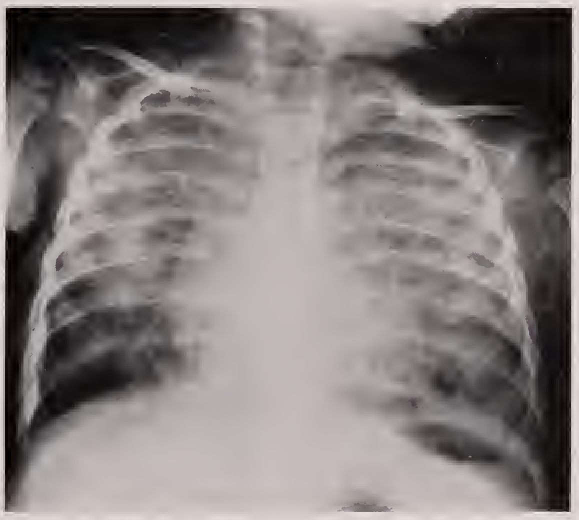

Fig. 5 — Disseminated disease caused by nocardiosis in young child.

that is characteristic of fungi, and histologic examination is used principally to rule out neoplasm rather than to identify the type of infection.

Identification of Specific Organism

The different types of granulomata can be distinguished from each other histologically only by finding the causative organism or substance, which is often not possible. In some cases — but not all — it is possible to identify Histoplasma capsulatum, Coccidioides immitis, or species of Actinomyces, Cryptococcus, Nocardia, and Blastomyces; but their absolute identity is seldom certain unless the available facilities are sufficient for reliable application of the fluorescent antibody technic. Even if cultures of the material are positive, the organisms may be very few. In cases of actinomycosis, careful study of the specimen of tissue or purulent material may reveal so-called sulfur granules, which are conglomerate masses of tangled filaments. However, as other organisms may produce granules indistinguishable grossly or in routine hematoxylin-and-eosin sections from those of actinomycosis, the diagnosis cannot be based on this finding alone.

Microbiologic Investigation

All of the foregoing may be summarized by saying that in nearly all cases the accurate diagnosis of specific fungous disease can be made only through isolating the organisms by microbiologic methods.

The Material Studied

Materials which may be submitted for study are sputum (three specimens desired), bronchial secretions and washings obtained bronchoscopically, gastric contents, body fluids (such as pleural, pericardial, or abdominal), pus, and caseous and other material obtained by curettement of draining sinuses. Tissue obtained by incisional or needle biopsy or by surgical resection (as in lung biopsy) requires special handling. The portion of tissue for the microbiologist is placed in a sterile container without fixative and is dispatched to the laboratory without delay. All surgically removed inflammatory and granulomatous tissue should be subjected to microbiologic study. Less frequently specimens of urine, stool, blood, marrow, or cerebrospinal fluid may also be cultured.

Staining Methods

When the microbiologist receives this material, all of which has been handled aseptically, he first examines by stain (gram, acid-fast, or Wright's) — or by alkaline preparation if the material is pus. Second, he cultures it for ordinary organisms, Brucella, tubercle bacilli, and fungi.

Animal Inoculation

Third, depending on the material and the results of the first procedure, he may or may not inject it into animals. If the material is something not easily obtained, such as tissue removed at operation, he should inoculate animals; if it is readily obtainable material, such as sputum and gastric contents, he may rely primarily on cultures. Animal inoculation is generally not effective in detecting fungi and is done primarily to isolate tubercle bacilli rather than fungi. Mouse inoculation may be useful for final identification of C. immitis or Cryptococcus neoformans.

Culture Methods

Specimens submitted for culture should include as much material as may be available. Often the causative organisms are few, and they may not be recovered from an inadequate sample. When several hundred milliliters of pleural fluid are removed, the entire specimen should be submitted to the microbiology laboratory to permit concentration of the organisms.

Since the extract of heart muscle with glucose (1 per cent) is suitable for isolation of many types of organisms and since the surgical obtainment of a specimen cannot be repeated, we have found it advantageous to incubate the plates at room temperature and at 30° and 37° C. In dealing with dimorphic organisms, such as Blastomyces or H. capsulatum, the yeast phase of the organism grows best at 37° C., the filamentous form at 25° C.

Actinomyces and Nocardia require special attention. For isolation of Actinomyces, cultures must be incubated anaerobically at 37° C. In our laboratory we use three different media — hormone agar, thioglycollate agar, and brain-heart infusion agar — all of about equal efficiency in recovering the organism. Nocardia grows aerobically; but because it is somewhat sensitive to the antibiotics used in culture media to inhibit bacterial growth, it too may be inhibited and difficult to recover. In our experience, Nocardia organisms grow fairly well on eosin-methylene blue, but not so luxuriantly as on blood agar plates without antibiotics. Because of this it is well to have material relatively free of contamination, such as secretions obtained bronchoscopically or pleural fluid.

Most pathogenic fungi will begin to appear in culture after three to 10 days of incubation, but considerable time (two to four weeks in some cases) may be required for final identification. If there is clinical evidence to suggest Actinomyces or Nocardia organisms as likely causative agents, a special request should be made for their isolation.

Fluorescent Antibody Technic

In detecting fungi, the value of the fluorescent antibody technic is limited. It is necessary to have on hand specific antisera for each organism to be tested, and these are not always available and often are not sufficiently sensitive or specific to give reliable information. In addition, organisms in the specimen may be too few for identification. The procedure is not available in all microbiology laboratories. When used properly, however, it may prove rapid and specific in its results.

WHAT'S YOUR DIAGNOSIS?

A 27-year-old man was admitted to the hospital on April 27, 1964, because of back pain of three weeks duration. He stated that he had fallen while skiing in the mountains near San Diego and had felt severe back pain immediately thereafter. He was able, however, to ride down the mountain seated in a car and consulted a Dr. Wagner in San Diego. He was hospitalized in The Clover Valley Hospital in San Diego .for three weeks and treated with traction. Following this he took a bus to Minneapolis. During the trip he again developed back pain and came directly from the bus depot in Minneapolis to the Emergency Room of a local hospital.

The pain was located in the "small of his back" and radiated into his right leg. His right foot was "asleep." The pain was constant and aggravated by coughing. He also complained of fever, chills, sweating and constipation during the previous week. A laminectomy had been performed three years previously.

Examination revealed a well-healed six-inch scar in the mid-line of his back. There was weakness of the extensor muscles of the right toes and loss of sharp sensation over the anterior aspect of the right lower leg. The straight-leg raising test was positive on the right at 30 degrees and on the left at 40 degrees. The right knee jerk was markedly diminished. The ankle jerks were equal and normal. Oral temperature was 103° F.

X rays of the spine showed narrowing of the interspace at L3-L4 with some droplets of contrast media in the spinal canal.

What's Your Diagnosis? See page 1048.

Troisier's Sign

(Advanced Carcinoma of the Stomach)

In advanced carcinoma of the stomach the left supraclavicular node is occasionally palpated. This is indicated as the sign of Troisier.

Unusual Deformity of the Ears:

Plastic Repair

JOHN B. ERICH, M.D.*
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An unusual congenital deformity of the ears is shown in Figure 1, in which the cartilages of the upper third of each ear are submerged under the adjoining skin at the side of the head. In this type of defect, there is no dermal covering on the posterior surface of the superior part of the auricle. Except for slight irregularity in contour, the cartilages in every other respect are normal. However, in this particular case, the lower two thirds of each ear protruded from the side of the head to accentuate further the deformity described above. As evidence of its rareness, I have seen only one other patient with this type of deformity.

Surgical Procedure

The surgical correction in the case presented herein was accomplished in two stages (Fig. 2). In the first operation, an incision was made in the skin immediately above the helix which was submerged under the tissues in the adjoining temporal region of the head. Working through this incision, the abnormal attachment of the ear was severed, thus leaving a raw surface on both the posterior surface of the ear and the side of the head. This area devoid of epithelium was covered with a split-thickness skin graft taken from the abdomen, the anchoring sutures being left long and tied over a bolus of gauze for immobilization of the graft. Six days later the sutures and gauze dressing were removed, exposing the healed skin graft.

Several weeks later, a second operation was performed to correct the protrusion of the lower two thirds of each ear. Before incising the skin, the position of the antihelix was outlined with an indelible pencil on the anterior aspect of each ear; this line was carried into the superior rather than the inferior crus. The skin was incised on the posterior surface of the ear directly opposite the pencil line just mentioned, the incision being carried upward to the skin-grafted area.

Retraction of the edges of the incision exposed the posterior surface of the auricular cartilages to which the position of the antihelix, as previously outlined in pencil on the anterior surface of the ear, was transferred with the aid of a hypodermic needle dipped in methylene blue. As a result of this process, a series of blue dots was produced on the exposed dorsal surface of the cartilage. Next, three parallel incisions two mm. apart were made through the full thickness of the cartilage and along the series of methylene blue dots. The small strips of cartilage intervening between these incisions were left intact. Before closure of the skin incision, mattress sutures were introduced through the anterior aspect of the ear to include the underlying cartilage, being placed about three mm. beyond the cut edges of the cartilage as shown in Figure 3. The skin incision was then closed by means of a running intracutaneous nylon suture which was easily pulled out on the fourth postoperative day. Each mattress suture was tied firmly over a small roll of cotton and left undisturbed for two weeks, at which time it was removed. The act of tying these sutures not only everts the cut edges of the cartilage to produce a convex antihelix, but also rotates the ear inward to correct the protrusive deformity.

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*Section of Plastic Surgery, Mayo Clinic and Mayo Foundation.

Comment

In a case such as this, I believe that mattress sutures offer a more effective means of forming the antihelix and eliminating the unnatural protrusion of the ears than do subcutaneous catgut stitches. However, mat-

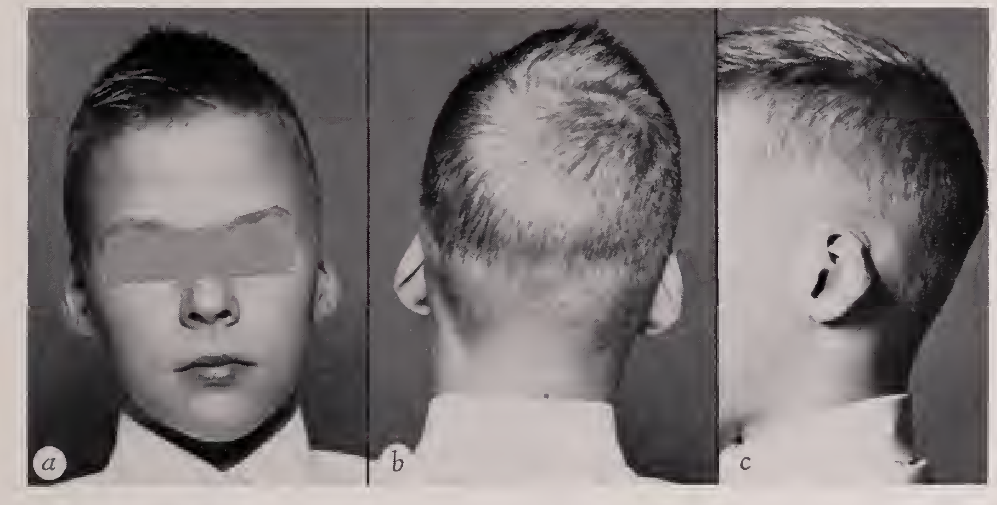

Fig. 1 — Bilateral deformity of the ears in which the cartilages forming the upper third of the ears are submerged under the skin at the sides of the head. (a) Anterior view. (b) Posterior view. (c) Side view.

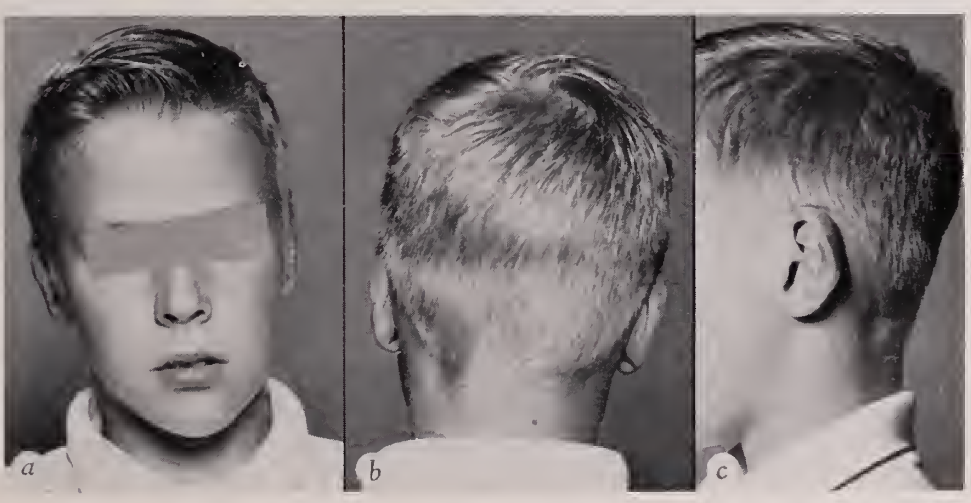

Fig. 2 — Postoperative result of surgical procedure performed in two stages. (a) Anterior view. (b) Posterior view. (c) Side view.

tress sutures, when left in place for two weeks, may produce some ulceration of the underlying skin. Although these ulcerations heal without any difficulty, they may leave small scars which are more or less conspicuous. This undesirable complication can be avoided by inserting the mattress sutures in such a way that they pass through cartilage only on the lateral side of the three parallel incisions, but through both cartilage and skin on the mesial side. In other words, these sutures in the lateral segment of cartilage are located beneath the skin over the ventral surface of the ear (Fig. 3); consequently, when tied, they can leave no scarring lateral to the newly formed antihelix. Admittedly, these sutures may produce some scarring on the mesial side, but since these scars are located in the concha, they are invisible except on close inspection of the ear.

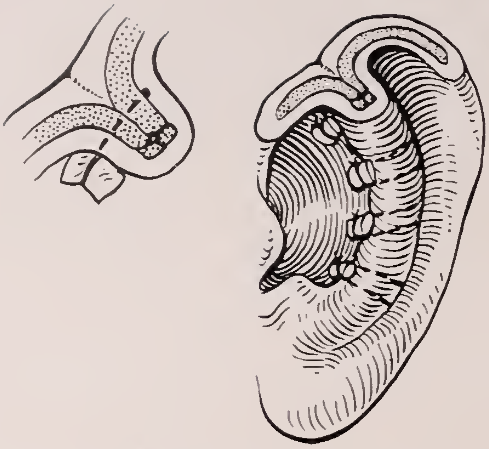

Fig. 3 — Mattress sutures used to bring out the antihelix and to correct protrusion of the ear are tied over tiny rolls of cotton on the mesial side of the antihelix, the rolls of cotton being located within the concha of ear. Inset shows how cut cartilages are brought back to back between mattress sutures to form the antihelix and to correct protrusion. Notice that two small strips of cartilage intervening between three parallel incisions are pushed forward under the skin of the antihelix; this makes a more rounded contour for antihelix than would be obtained if an ellipse of cartilage had been excised.

The auricular defect described in this paper is extremely uncommon but can be corrected satisfactorily by the surgical technics which have been presented.

ANSWER TO WHAT'S YOUR DIAGNOSIS

(From page 1045)

When the patient's temperature was taken with a nurse present, it was invariably found to be normal. He seemingly had pain, requiring the use of Demerol; but if he thought he was unobserved, he moved about the room freely. The San Diego doctor's name and the hospital there both proved to be nonexistent. When questioned about his previous hospitalization, he "improved" dramatically and left the hospital against advice. Then he promptly went to the emergency room of another hospital where the same process was repeated.

If this patient follows the pattern set by others with Munchausen's syndrome, he will become well known to hospitals and physicians across the country. The name of this syndrome is derived from Baron Munchausen,* a mythical figure, who traveled about the country telling strange and unusual tales.

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*See Page 1064, Munchausen Syndrome.

"Baron Munchausen's Narrative of His Marvelous Travels and Campaigns in Russia" translated from German by Rudolph Eric Raspe in 1785.

In an age when we have perfected ways to destroy the world before we understand fully how to preserve it, the conduct of foreign affairs is an overwhelming responsibility.

—Karl E. Mundt, U. S. Senator, South Dakota, Foreign Relations Committee

Management of the Chronic Asthmatic

LOWELL L. HENDERSON, M.D.*
GILES A. KOELSCHE, M.D.*
Rochester, Minnesota

MANY PATIENTS with asthma are seldom entirely free of symptoms. They live and work at a low energy level. Even with medicaments at hand, treatment is often abortive and sporadic — sometimes because of a guilt feeling about taking too much medicine or fear of becoming addicted to it. They make emergency trips to the hospital or rouse the physician for a 3:00 a.m. house call when the situation becomes intolerable, and then limp along until the next exacerbation.

Exertion, exposure, and chronic cough keep their bronchi persistently irritable; and while they may be assiduous in avoiding items that have been found positive on allergy skin tests, they are likely exposing themselves to various other respiratory irritants.

Proper handling of this type of patient prevents a great deal of morbidity, sometimes allowing even the semi-invalid to become economically self-sufficient. Much like the diabetic, he must be made acquainted with the need for continuous management and encouraged to learn as much as possible about the vagaries of the disease so that he can manage each new situation as it arises without undue dismay or panic.[1]

The physician, in approaching the management of these patients, should consider their general health, status, and particularly other respiratory diseases or complications, such as sinus infection, nasal polyps, and bronchiectasis. If surgery appears necessary, there may be need to postpone it until the asthma is satisfactory controlled.[2] If emphysema is found superimposed on chronic asthma, that calls for special consideration. However, the measures for the underlying asthma still apply.

Investigation

Asthma is like all other diseases in requiring a careful history as the foundation of the investigation. The patient's work, his home activity, and his hobbies should be considered. He should be questioned in detail about his likes and dislikes in foods, what drugs and toilet articles he is using, and what he has observed that seems to make his symptoms worse. His attention should be called to the fact that many nonspecific things such as cold air, detergent powder, temperature changes, and paint odors must come under the same suspicion as the more commonly discussed skin-test items such as dog hair, house dust, and ragweed pollen. Skin tests may be performed for confirmatory information, but these are best confined to the inhalant allergens. Results of skin tests for foods are capricious; and information much more accurate can be obtained, albeit more slowly, by trial-and-error dietary manipulation. Regardless of the outcome of skin tests, it must be kept in mind that anything which adds to atmospheric contamination is a potential hazard. The patient must be made to realize that many items may add to the irritation of the respiratory membranes while not necessarily acting in a strong enough manner to cause asthma at the time of contact.

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*Section of Medicine, Mayo Clinic and Mayo Foundation.

Environmental Control

It should be explained carefully to the patient that avoidance of an offending item gives better results than desensitization to it; that desensitization is not a cure; and furthermore, that in the face of continued heavy exposure it is usually insufficient to afford relief.

Elimination Measures

On the other hand one must not let his enthusiasm run away with him in discussing elimination measures with the patient. To outline a rigid program that would result in barracks-style living for him is quite a different thing from going home and doing the same in one's own house. Better cooperation usually results if a reasonable attempt is made to apply the easier measures first. We tell the patient that regardless of his skin-test results he should keep out of the house any pets with hair or feathers, such as dogs, cats, canaries, and parakeets. The suggestion can be made to board these elsewhere for a month or so; after that, permanent removal of them is less painful.

The Bedroom

Since the patient spends several hours of each 24 in the bedroom, this place should be made as lint-free and dust-free as possible. Synthetic pillows are recommended. The mattress should be covered with a plastic cover and any fuzzy cotton and wool blankets, old quilts, and down comforters eliminated. Venetian blinds are dust-catchers and should be removed. Only washable throw rugs should be retained here; and the patient is urged to eliminate carpeting and fiber pads, particularly if his skin tests are positive for cow or hog dander which may be in the fiber rug cushion, or to house dust which the rug harbors.

Protective Measures

An oronasal mask with a satisfactory filter should be advised when the person's work necessarily exposes him to dusts such as those encountered in farm activities. There are now available some less repulsive-looking, lighter-weight products which the housewife may be willing to wear when cleaning and dusting.

Although a temporary compromise is sometimes expedient in regard to some of the above measures, we take an uncompromising stand against smoking.[3] We have no concern about results of skin tests for tobacco or tobacco smoke and indeed have ceased making such tests. We explain to the patient that the chemicals in tobacco smoke act upon the respiratory membrane as direct irritants. We impress on these patients that the full beneficial effect of abstinence is realized only after about six months, and that lack of improvement which they may have experienced in two or three weeks of abstinence is no argument for continuing smoking.

The patient is cautioned against exposure to cold drafts and sleeping in a cold bedroom. He is advised to avoid sudden changes of temperature such as going from a warm building into the cold or vice versa. A wadded handkerchief held over the mouth and nose as he makes such a change helps to avoid thermal shock to the bronchi. If the patient lives in air-conditioning, similar shock may be obviated by having the control set no colder than 8° F. below the outside temperature.

Humidity

One problem that is difficult to resolve satisfactorily is the dryness of the air in the northern winter. The relative humidity of air indoors, after being heated from zero temperature outside, may be as low as eight to ten per cent. (In contrast, the relative humidity of desert air may amount to 15 per cent.) A desirable humidity level is in the range of 40 to 50 per cent, and this cannot be achieved under conditions by any method currently available. In some of the more severe cases we have felt justified in recommending a sojourn in a warmer climate for two or three of the more severe winter months.

Standard Medication

Regardless of other measures, the patient is likely to need some medication from time to time. "Too little and too late" characterizes the mistakes often committed in this regard. We try to give our patients some understanding of the pharmacologic actions of the drugs commonly employed and encourage them to initiate adequate medication early and continue it regularly as long as symptoms persist. Most of the medicaments fall into one of two groups: bronchodilators (quick-acting or long-acting) and expectorants. The patient usually is supplied with a preparation of each type.

Bronchodilators

Ephedrine

For the patient who is recurrently and persistently wheezing, the long-acting bronchodilator ephedrine is the mainstay of treatment. It is effective as administered orally, its action starting about 20 minutes after ingestion and persisting four to six hours. The standard 25-mg. capsule is quite satisfactory. There are also numerous ephedrine compounds, usually containing a small amount of sedative and approximately 100 mg. of aminophylline. These are quite acceptable. We prefer the tablet form, such as Amodrine (aminophylline, racephedrine, and phenobarbital) or Tedral (theophylline, ephedrine, and phenobarbital), so that the dose can be fractionated if desired. When the asthma is less severe but still persistent, we advise the patient to take half a tablet every four hours rather than a full dose at less frequent intervals.

Men with borderline prostatism may suffer retention due to the relaxing effect of ephedrine on the urinary bladder. In these cases the ephedrine-like drug methoxyphenamine (Orthoxine) may control the bronchospasm with less side effect. This is given in a dose of 100 mg. orally every four hours and is also available in combination with aminophylline.

Aminophylline

Aminophylline is also an excellent long-acting bronchodilator but seldom can be depended upon solely, since oral administration of an adequate dose usually eventuates in nausea. We find it most useful in the form of rectal suppositories or enemas to be used at night as an adjunct to other treatment during periods when the asthma is worse. Even in this form it may cause anal irritation if used oftener than three or four nights a week.

Aerosols

Quicker but less persistent relief than ephedrine affords may be obtained by use of nebulized bronchodilators. Often one or two inhalations tide the patient over a period of dyspnea associated with inadvertent exposure or overexertion, or allow him to get back to sleep quickly if he is awakened with choking or chest tightness. The nebulized material in the pressurized bottles has proved convenient; however, it is more expensive and some persons find it more irritating to the throat than aerosols delivered with hand-bulb nebulizers. Among the latter we have found the DeVilbiss No. 40 to give good results, especially if the side cork is removed. We most often use isoproterenol (Isuprel) in its original strength of 1:200, or have the patient dilute it in the nebulizer with an equal volume of tap water, making a 1:400 solution. Epinephrine in a 1:100 solution is also quite satisfactory but has slightly more pressor effect.

In some cases the sputum becomes darker and heavier periodically, leading to an exacerbation of the asthma. Often these attacks can be aborted by increased, regular use of a nebulized bronchodilator. We instruct the patient to use this four to six times a day, inhaling from the nebulizer each fourth breath for a period of 20 minutes. Pressure furnished by oxygen tank or an electric pump may be desirable if frequent aerosol treatment is necessary, especially if the patient is debilitated.

We have never found tablets of isoproterenol administered sublingually to be very helpful, although some patients are able to obtain relief from milder attacks with this preparation.

Parenteral Medication

Self-administration of epinephrine by injection seems to be one of the more neglected kinds of treatment for quick effect, and yet one of the most helpful to the patient with chronic asthma. Most have experienced some degree of panic that comes with the mounting dyspnea while awaiting the arrival of the physician. Often the assurance of relief that epinephrine can provide when the patient's other medications have failed him is the key to relieving much of his anxiety. On the other hand, instruction in this measure is useless unless we overcome his reluctance to inject himself with a drug which he has come to regard with awe and respect. He must also be reassured that the small bubble of air that may be inadvertently injected is not going to cause his sudden demise. We instruct the patient to give himself three or four doses of 0.25 to 0.35 ml. at intervals of 20 to 30 minutes. If he does not obtain adequate relief after two or three series, he should notify his physician. A wide selection of disposable syringes and needles is now available. For frequent use, the cheapest combination is a glass tuberculin syringe with reusable steel needles and a 30-ml. rubber-capped vial of 1:1000 epinephrine. Perhaps the handiest outfit is the Wyeth metal syringe into which is fitted a disposable unit consisting of a 1-ml. cartridge of 1:1000 epinephrine with needle attached.

Expectorants

The second important group of antiasthmatic medicaments are the expectorants. Mucus is a dominant factor, both directly by its obstructive action and indirectly through the coughing it provokes. Dehydration worsens its effect, and we urge the asthmatic to drink at least 10 glasses of water each day. Usually some increase of expectorant action is needed, and nothing rivals iodides for this purpose.

We ordinarily direct the patient to take 10 drops of saturated solution of potassium iodide in a glass of water three times a day. We forewarn him that he may experience an eruption. If it is acneiform, he may stop taking the drug for a few days and then resume with a smaller dose, which may be tolerated. If the eruption is a pruritic rash, however, it will likely recur with any dose of iodide. Occasionally an organic iodide compound is tolerated under these conditions; but unfortunately, no other drug is nearly so effective an expectorant as iodide, although ammonium chloride and guaiacolate compounds such as Robitussin and Quibron (which includes theophylline) may be helpful.

Adrenal Corticosteroids

A third group of drugs — which we have placed purposely in that order — are the steroids. Only after all of the above measures have been utilized to the utmost and proved insufficient do we feel that the use of steroids is justifiable.

Oral Steroid

It is sometimes possible to help the patient avoid hospitalization by giving him triamcinolone or its equivalent in a dose of 8 mg. every six hours for a few days and rapidly tapering off in 10 to 14 days. In the absence of any strong contraindications, little harm is likely to result from this treatment even if it becomes necessary once or twice a year. Another problem is the condition which is relieved only by such a course of steroid therapy but flares each time it is discontinued. Fortunately these situations are exceptional, but we have to settle for the smallest maintenance dose possible. When combined with all of the conservative measures, 1 mg. once or twice daily may prove sufficient.

Steroid Aerosol

We have been interested in the local application of steroids by nebulization in the hope of achieving the greatest anti-inflammatory effect with the least systemic reaction.[4] It is likely, however, that at least some of the steroid is absorbed from bronchial secretions that are brought up and swallowed; so it is possible that any beneficial changes observed are due to this fraction. Some of the recently marketed products deliver a satisfactory steroid aerosol; and although they are moderately expensive, it seems reasonable to try one of these in the problem case before going on to oral administration of steroids for an indefinitely prolonged period.

Adjuncts

Antitussives

In addition to medicaments suitable for combatting the asthmatic condition directly, there are certain other frequently used adjuncts. If the patient has a persistent racking cough, we are not averse to using a codeine preparation for a few days; but this medication should not be continued over a long period simply for the cough which is the usual component of asthma. We have used some of the non-narcotic drugs more freely, including pipazethate (Theratuss) and levopropoxyphene (Novrad). Some patients obtain adequate relief with aspirin, which probably simply diminishes their sense of tracheobronchial irritation. Of course definite inquiry should be made to avoid giving this drug to aspirin-sensitive patients, to whom it could prove fatal.

Tranquilizers

Tranquilizers and sedatives are helpful in many cases, and we do not hesitate to use them as the need arises. Chloral hydrate in a dose of 15 grains at bedtime provides useful sedation reasonably free of side effects, including allergic sensitivity. Barbiturates, promazine (Sparine), and chlordiazepoxide (Librium) are useful adjuncts, particularly for daytime use.

Medications Not Favored

Most physicians realize that morphine is best avoided in asthma; but unfortunately another narcotic, meperidine (Demerol), is used all too often. Although it soothes the ordinary asthmatic, it can also cause addiction and, if used without sufficient other measures, sustains a false sense of well-being while the basic condition is becoming worse. Belladonna and its derivatives are best avoided also, since they dry out secretions and often cause stickiness of mucus and increased coughing. We have seen numerous serious toxic reactions to Fowler's solution (potassium arsenite) and believe that the risk of using arsenical preparations is not justified.

Densensitization

Desensitization procedures are rarely needed, nor indeed would they prove helpful in most cases of chronic perennial asthma. As mentioned earlier, the provocative factors in many cases are acting as mechanical, chemical, or thermal irritants, and no allergic process is involved. In the majority of the remainder, where clinical observations corroborated by positive skin tests indicate that the process is allergic, removal of the offending agents or institution of avoïdance measures gives better results than desensitization. However, desensitization may provide additional help for some patients sensitive to house dust and may also be considered in certain other situations of allergenic exposure.

Conclusion

Once more we may point out that our maintenance program for the chronic asthmatic consists in teaching him to take care of himself by instituting the proper avoidance measures, using medication judiciously, and being satisfied with something short of a cure. If these aims are achieved, the patient usually is able to pursue a gainful occupation and avoid becoming a frustrated invalid.

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IT'S THE LAW

*Union May Refer Members to Attorneys**

A union may lawfully advise injured workers not to settle their claims without consulting an attorney and it may recommend a specific attorney. A majority of the U. S. Supreme Court ruled that a state law prohibiting such activity was an unconstitutional interference with the rights of the union members to freedom of speech, petition, and assembly under the First and Fourteenth Amendments.

This union activity had been enjoined by a state court on the ground that it amounted to unlawful solicitation of clients for attorneys and unauthorized practice of law. The union selected and approved sixteen regional attorneys. Its representatives contacted injured workmen and advised them not to settle their claims before consulting an attorney. They also recommended the appropriate regional attorney and advised the workman that this attorney was the only one approved by the union in the region. It was admitted by the union that the effect of this activity was to channel legal employment to these particular attorneys.

Justice Clark dissented vigorously, stating that the activity of the union contravenes both the accepted ethics of the legal profession and the statutory and judicial rules of accepted conduct. He also said that the majority decision relegates the practice of law to the level of a commercial enterprise. Justice Harlan joined in the dissent.

Brotherhood of Railroad Trainmen v. Virginia, 84 S. Ct. 113 (U. S., Apr. 20, 1964)

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*See Editors Soliloquy Page 1085

What we earnestly aspire to be, that in some sense we are.—Anna Jameson

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Make yourself an honest man, and then you may be sure there is one rascal less in the world.—Carlyle

Ski Fracture of the Metacarpals

One of the First Sports Injuries Reported in the Medical Literature

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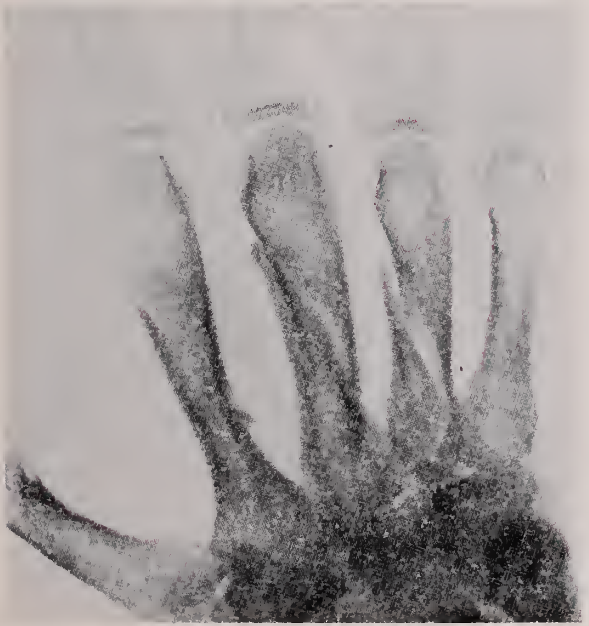

Fig. 1 — Spiral fractures of metacarpals II, III, and IV. (From Blauel.)[1]

ONE OF the first sports injuries to be specifically described in the medical literature is ski fracture of the metacarpal bones. In 1909, Blauel[1] reported a fracture of the metacarpals caused by skiing. He described the mode of injury in his patient as follows: as the skier went downhill, his trailing ski pole struck a tree, violently twisting the grasping and thonged hand. The torsion of the pole in the tightly clenched hand caused spiral fractures of the second, third, and fourth metacarpals (Fig. 1).

Logròscino,[2] however, has not been able to confirm this method of injury, as originally described by Blauel, but has insisted that the fracture occurs as the skier falls forward onto his clenched hand which is grasping the grip of the ski pole (Fig. 2*a* and *b*). The surface is usually hard-packed snow or icy snow. The outer edge of the hand, that is, the ulnar side, strikes first, and as the skier rolls forward down the hill the metacarpals fracture with a torsional force. The fracture is rather specific for ski injuries, being spiral rather than transverse, and usually involves the lateral four metacarpals either singly or in combination (Fig. 3). If multiple, the fractures occur in an oblique fashion from distal to proximal as they pass from the radial to the ulnar aspect of the hand (Fig. 1).

Incidence

Metacarpal fractures occur more commonly from skiing than from any other sport, and yet they are an uncommon injury even in skiing.

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In 1943 Moritz[3] reported on his extensive experience at Sun Valley, Idaho. He stated that over a three-year period he saw only 14 patients with metacarpal fractures as a result of skiing.

Morrison and Coughlin[4] found only four skiers with fractures of the metacarpals in their community in the Berkshire Mountains in the year 1948. They emphasized that this fracture seemed more common in Italy and Switzerland than in the United States.

Allaria,[5] in 1950, writing on studies of medical and surgical aspects of sports from the Institute Codivilla-Putti at Cortina d' Ampezzo, reported that injuries of the upper extremity represented 26.2 per cent of ski accidents, and that injuries of the hand represented 5.6 per cent.

Logròscino,[2] in 1937, wrote on 12 cases of metacarpal fractures from skiing at Cortina d'Ampezzo.

Although skiing produces fracture of the metacarpals less commonly than, for example, fracture of the tibia, it is reasonable to expect an increasing occurrence of metacarpal fractures, along with other injuries, as the almost phenomenal growth of this sport takes place.

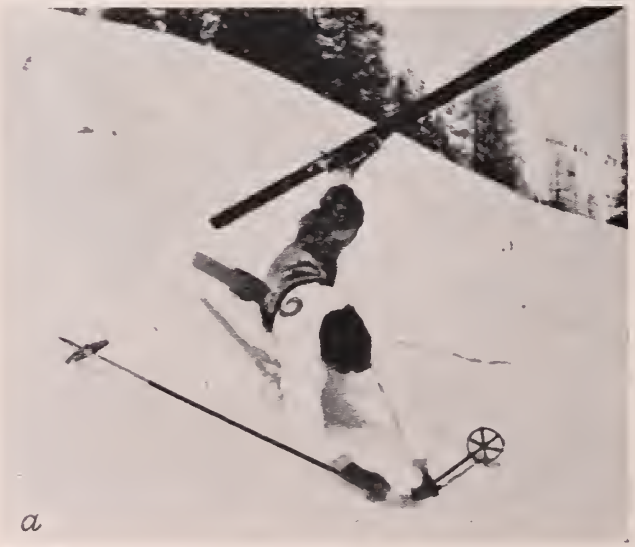
Treatment

This type of metacarpal fracture is a specific skiing injury, readily recognized both clinically and radiographically, and it is treated in a specific way. The application of a dorsal splint to the hand and wrist is usually all that is necessary. The splint may be of plaster of Paris or of any other properly fitting and firm material. Splinting should be maintained until all swelling subsides and fibrocartilaginous callus forms at the fracture site. Finger exercises should be encouraged during this period. When callus has formed, the hand and wrist may be gently mobilized and within eight weeks most of the disability will have cleared.

Function and anatomic restoration are usually excellent following this fracture. Angulation of the metacarpals seldom occurs, and it can be readily corrected by manipulation if it does. Slight but definite shortening may be expected, but this is not a disability unless it becomes pronounced. Lipscomb[6] believes that shortening of more than 1 cm. should be corrected by manipulation, and fixation using light traction or Kirschner wires should be used.

Report of Case

A 45-year-old male skier fell forward onto a hard, icy slope during downhill skiing, striking the knuckles of the left hand which was grasped about his ski pole in the usual fashion. Pain occurred immediately and roentgenograms revealed multiple metacarpal fractures. The appearance varied from the usual in that the fifth metacarpal was fractured (without displacement) more distal (rather than proximal) to the fractures of the third and fourth metacarpals (Fig. 4*a*).



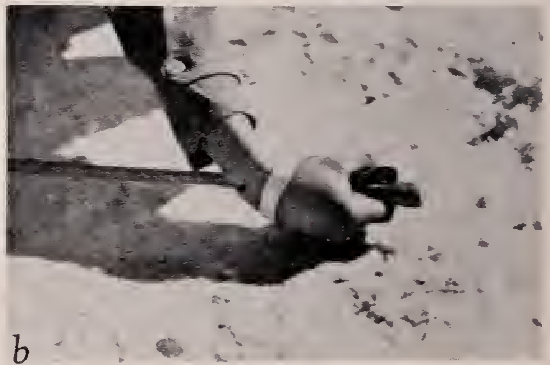


Fig. 2*a* and *b* — Mechanism of production of ski fracture of the metacarpals. Note fall forward in *(a)* (usually on hard or icy snow), and striking of knuckles, producing torsional force, in (b).*

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*From Logròscino, Domenico: Fratture dei metacarpi da sci. Chir. org. movimento, 22:479-486, Mar., 1937. By permission of the publisher, L. Cappelli, Bologna.[2]

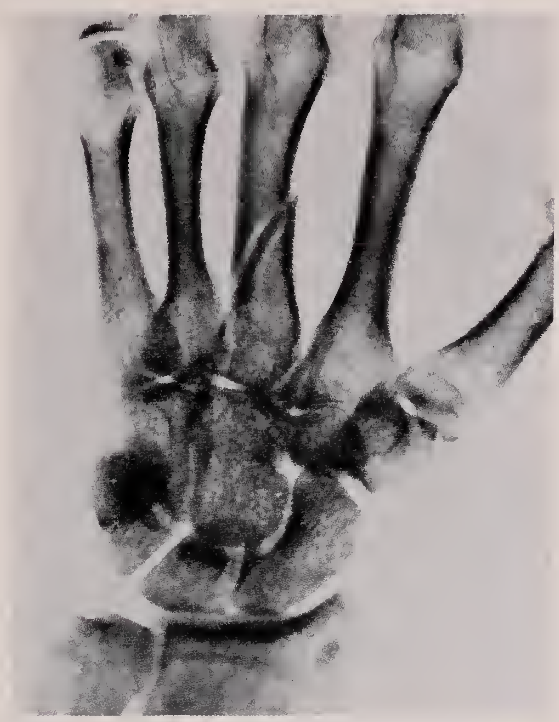

Fig. 3 — Classic ski fracture as illustrated by Logròscino. Only the third metacarpal is involved. See note on page 1056.*

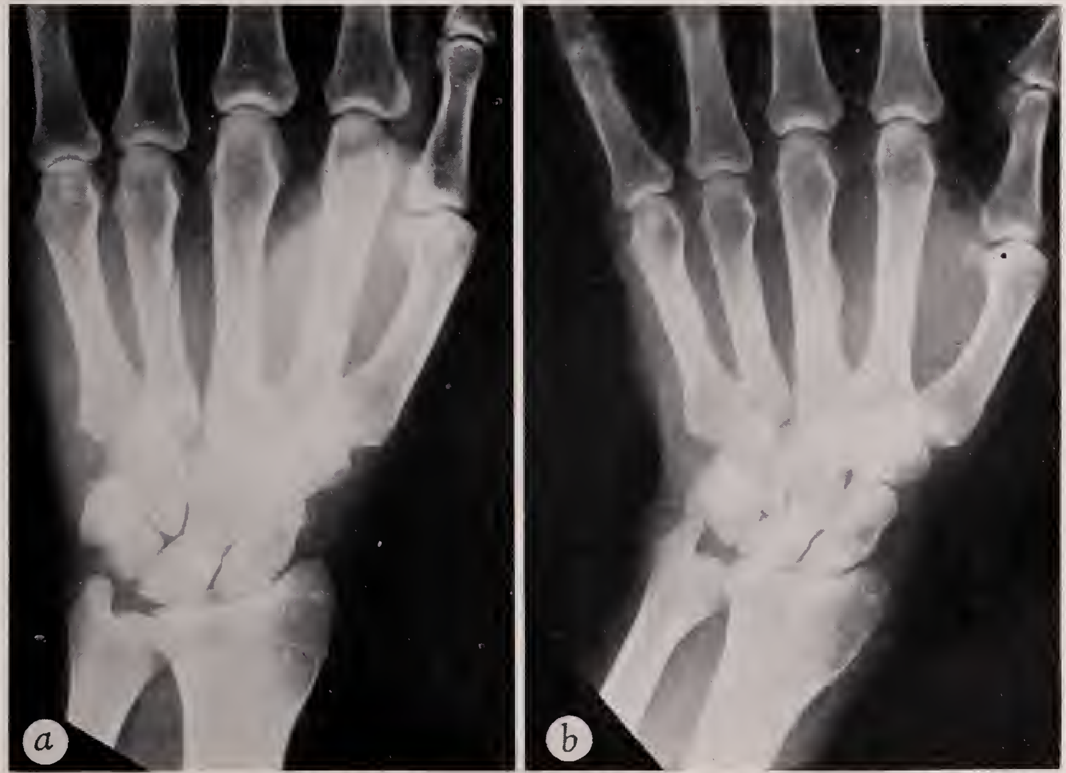

Fig. 4 — *(a)* Fractures of metacarpals III, IV, and V from fall forward on left hand grasped about grip of ski pole. *(b)* Ten weeks after fracture. Note bony callus with very minimal shortening of metacarpals III and IV. Patient has normal function and no pain.

Treatment consisted of a plaster-of-Paris splint applied dorsally on the forearm and wrist down to the metacarpophalangeal joints of the hand. It was held by an elastic bandage which encircled the dorsal splint and the volar surface of the forearm and hand which was covered with cotton padding. This was retained for four weeks, and limited function then was encouraged. Ten weeks after fracture the metacarpals were healed in excellent position and function was normal (Fig. 4*b*). Very minimal shortening of the third and fourth metacarpals could be measured. Five years later, function was unimpaired and strength was normal. There was no pain.

Other Injuries of the Hand

Sprains and dislocations of the interphalangeal and metacarpophalangeal joints occur during skiing from falls and from entanglement in tows and lifts. These are really not specific to skiing. But injury to the base of the first metacarpal is related to skiing in this fashion: the skier falls backward, not forward as in metacarpal fractures just described, and either strikes his thumb directly, or strikes the ski pole, which transmits a leverage force to the base of the first metacarpal. Allaria believes the usual resulting fracture to be transverse through the shaft of the first metacarpal at its junction with the proximal metaphysis. Less likely, a fracture-dislocation, of the Bennett type, may occur.

Summary

In 1909, Blauel first described a specific injury to the metacarpals caused by skiing. These fractures have been occurring with regularity since then. The rapidly growing interest in skiing as a sport, especially since World War II, will undoubtedly acquaint more physicians (and their skiing patients!) with this fracture. We have added a report of a ski fracture of the metacarpals with a five-year follow-up.

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Pliny's* Treatment for Paratonsillar Abscess

For the treatment of quinzy, Pliny recommended argemonia* in wine or a decoction of hyssop** boiled with figs to be used as a gargle. As a gargle he also recommended the juice of cinquefoil† as being beneficial to all infections of the pharynx. Verbascum‡ in wine was another remedy for inflammation of the tonsils.

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*Argemonia — This is known popularly under the name of prickly poppy, Devil's Fig, or Jamaica Thistle. The whole plant abounds in a milky acrid juice which turns yellow on exposure to the air, and has been used locally as a domestic remedy for warts and various skin disases. The plant contains the alkaloids of protopine and berberine.

**Hyssop — This is an aromatic leaf used by the priesthood in the time of Dioscorides. It was spoken of as a holy herb. It contains volatile oils.

†Cinquefoil — This was one of the simplest remedies which Hippocrates gave for the ague. In later practice Dioscorides prescribed three leaves for a tertian fever and four for a quartan. The leaves in both cases were to be mixed with an amulet of three spiders.

‡Verbascum — This was called flannel leaf and was used in catarrhal conditions of the respiratory tract.

*See Minnesota Medicine, June, 1964, Page 716.

Take Time TO GIVE — It is too short a day to be selfish.

In every work of genius we recognize our own rejected thoughts.—Emerson

Familial Periodic Paralysis

● A
● Review

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FORMERLY, ONLY one kind of periodic paralysis was recognized — the sporadic or the familial disease with episodic weakness of skeletal muscles considered to be caused by low serum potassium. Today, in addition to this hypokalemic form, other types of familial periodic paralysis are recognized; these include normokalemic periodic paralysis, hyperkalemic periodic paralysis, hyperkalemic periodic paralysis with myotonia, and paramyotonia with periodic paralysis. These disorders are similar in that they occur in young individuals, have predominant symmetrical involvement of the limb muscle with an attack, have an onset of an attack during the night or during periods of rest that follow exertion, and have a duration of weakness from several hours to several days. These disorders usually are familial, although occasional cases are identified in which there is no evidence of familial occurrence.

There are other causes of periodic weakness that should be distinguished from these forms of familial periodic paralysis. Hypokalemic periodic paralysis occurs with thyrotoxicosis, primary aldosteronism, excessive potassium loss from renal or gastrointestinal disease, various medications, and licorice intoxication. Four disorders in which muscle weakness develops during activity are myasthenia gravis, the myasthenic syndrome, glycogen-storage disease of muscle (for example, McArdle's disease), and familial paroxysmal myoglobinuria (Meyer-Betz disease). In the last two conditions, painful muscle cramps occur with a limited exercise tolerance. The weakness in familial periodic paralysis occurs with rest, and this helps to distinguish it from these four disorders. Finally, patients with conversion hysteria may also give a history of episodic weakness.

Hypokalemic Periodic Paralysis

Musgrave,[1] in 1727, described a case of a 31-year-old woman with classic periodic paralysis. Goldflam,[2] in 1897, first drew attention to the central vacuoles seen in the muscle fibers of patients with this disorder. In 1934, Biemond and Daniels[3] found a low value of serum potassium in patients with paralytic attacks, and Aitken and associates,[4] in 1938, found that the administration of potassium helps abort and remit attacks.

Clinical Manifestations

Hypokalemic periodic paralysis may be sporadic or familial and usually begins in patients who are in the first or second decade of life. With advancing age, attacks become less frequent. More often than was formerly recognized, some permanent weakness develops. Typically, an attack may be well advanced when the patient awakens in the morning. Often the patient gives a history of eating a large meal on the preceding day. In the daytime, weakness may begin during a period of rest that follows heavy exertion. An attack usually may be induced by the administration of 150 gm. of glucose orally and by the administration of 15 units of regular insulin subcutaneously. Spontaneous attacks may last from several hours to several days. Sweating, a feeling of heaviness of the extremities, and paresthesia may herald its onset. The attack may be aborted or lessened by what patients refer to as "walking it off." Muscles that are involved are usually those of the limb and less frequently axial and bulbar muscles; sphincters are unaffected. Tendon reflexes are either diminished or absent. Observant patients may report increased size and firmness of muscles. The amount of urine produced decreases with an attack and increases with improvement of an attack.

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Metabolic Abnormalities

It is becoming more evident that the paralytic attacks are explained inadequately by the alteration in serum potassium. The initial observations that the level of serum potassium was lowered with an attack of weakness[3] and was associated with a decreased urinary output of potassium[5] suggested a selective movement of potassium from the extracellular space into the muscle fiber with resulting hyperpolarization and weakness. Persons with periodic paralysis have been described, such as the family reported on by Tyler and associates[6] in 1951, in which the serum potassium remains normal during an attack. Even in the hypokalemic variety of periodic paralysis, significant muscle weakness is present at serum potassium levels that, in the normal person, would not be associated with muscle weakness.[7] Furthermore, clinical improvement may begin before the serum potassium has reached its lowest point. Special studies, particularly by Shy and co-workers,[8] have not demonstrated a cationic influx into the muscle fiber or the expected hyperpolarization.

Conn's[9] finding of elevated excretion of urinary aldosterone in a patient with periodic paralysis has not been substantiated in familial hypokalemic periodic paralysis;[8-10] injection of aldosterone has failed to produce weakness.[8] Aitken and associates,[4] in 1938,

TABLE I
Clinical Features in Familial Periodic Paralysis*

Clinical features	Hypo-kalemic	Normo-kalemic	Hyper-kalemic	Hyperkalemic with myotonia	Para-myotonia
Inheritance	D, R, S-L, S	D, S	D, S	D	D, S
Onset of disease, decade	1, 2	1, 2	1	1, 2	1
Attack					
Onset	Night	Night	Day	Day	Day-night
Duration	Hr.—days	Hr.—days	Hr.—days	Hr.—days	Hr.—days
Positive Chvostek's sign	0+	0+	+	+	—
Diaphoresis	0+	0+	0+	0+	0+
Heaviness of extremity	0+	0+	0+	0+	0+
Paresthesia, hands and mouth	0+	0+	0+	0+	0+
Muscles affected					
Limb	+	+	+	+	+
Respiratory	0+	—	0+	—	—
Bulbar	0+	—	0+	—	—
Muscles enlarged with attack	0+	0+	?	?	?
Hyporeflexia-areflexia	+	+	+	+	+
Percussion myotonia	—	—	? or —	+	+
Dystrophy	0+	0+	0+	—	—

*D = dominant; R = recessive; S-L = sex-linked; S = sporadic; + = present; 0+ = may be present; — = absent; ? = unknown.

TABLE 2
Factors Influencing Attacks in Familial Periodic Paralysis*

Factors	Hypo-kalemic	Normo-kalemic	Hyper-kalemic	Hyperkalemic with myotonia	Para-myotonia
Rest after exertion	W	W	W	W	? or 0
"Walking it off"	I	I	I	I	I
Cold weather	W	?	W	W	W
Cooling extremity (16° C. for 20 min.)	W	?	?	0	W
Administration of glucose, oral (150 gm.) insulin, subcutaneous (15 units)	W	0	0	W	0
Diet					
High carbohydrate	W	?	?	0	0
High sodium	W	?	?	0	0
Low sodium (1 gm. NaCl)	I	0	? or W	? or W	0
High potassium	I	0	W	W	0
Low potassium	W	?	0	I	0
Medications					
Potassium chloride (30 ml. of 25%, 4 times/day)	I	0	W	W	0
Aldosterone	0	?	?	?	?
Epinephrine	W	?	?	?	?
Mineral corticosteroids	W	?	I	I	?
Spironolactones	I	?	?	?	?
Hydrochlorothiazide (50 mg. intravenously)	0	0	I	I	0

*I = improved; W = worse; 0 = no effect; ? = effect not known.

TABLE 3.
Laboratory Findings With Attacks in Familial Periodic Paralysis*

Findings	Hypo-kalemic	Normo-kalemic	Hyper-kalemic	Hyperkalemic with myotonia	Para-myotonia
Serum					
Potassium	Low	N	High	High	? or High
Sodium	N	N	N	N	N
Chloride	N	N	N	N	N
Calcium	N	N	N	N	N
Intracellular potassium	N	?	?	?	?
Urine volume	Low	?	? or Low	?	?
Intracellular volume	Increased	?	?	?	?
Intracellular vacuoles	Present	Present	?	?	? or N
Glucose tolerance test	High	N	?	?	?

*N = normal; ? = unknown.

suggested a basic metabolic error in carbohydrate metabolism. More recently, Shy and associates[8] postulated that a defect in the synthesis of glycogen was the primary abnormality, with alterations in potassium concentration being secondary.

Provocative Tests

Diagnostic provocative tests of hypokalemic periodic paralysis may include (1) a large meal, (2) physical exertion followed by rest, (3) oral administration of 150 gm. of glucose with subcutaneous administration of 15 units of regular insulin, and (4) subcutaneous administration of 0.6 to 1 ml. of epinephrine (1:1000).

Treatment

Unfortunately, treatment is inadequate in many cases. The following measures can be used: (1) smaller more frequent meals that are low in salt (40 to 60 mEq. sodium in 24 hours) and high in potassium (300 mEq. of potassium in 24 hours); (2) added potassium chloride (30 ml. of 25 per cent potassium chloride four times a day), (3) Spironolactones (Aldactone-A) (400 to 600 mg. per day), and (4) possibly thiamine.[11] Serum electrolyte changes should be followed to recognize and prevent hyperkalemia.

Normokalemic Periodic Paralysis

In 1951, Tyler and associates[6] studied a kinship of 33 persons with periodic paralysis in which "clinically the process is nearly identical with previously described cases of periodic paralysis whether hereditary or apparently sporadic" but different in that no hypokalemia with attacks was found. The lowest value for serum potassium recorded was 3.5 mEq. per liter. Oral therapy with potassium salts during paralytic attacks was ineffective. In this family, as well as in another described by Poskanzer and Kerr,[12] central vacuoles of muscle fibers were seen. These authors described a favorable response to the administration of sodium chloride.

Hyperkalemic Periodic Paralysis

In 1956, Gamstorp[13] described a Swedish kinship in which periodic paralysis was associated with elevated levels of serum potassium. She identified this condition as a separate disease and called it adynamia episodica hereditaria or, in other words, familial periodic paralysis. The episodes of muscle paralysis seemed clinically similar in most ways to those of the hypokalemic variety except that the tendency for an attack to occur during rest after exertion was more pronounced. She and others[14,15] have shown the provocative effect that the taking of 1 to 10 gm. of potassium chloride by mouth can have in the production of weakness and the improvement that can occur with frequent small meals that are low in potassium. Mineral corticosteroid preparations and hydrochlorothiazide can be used to lower the serum potassium level and to produce remission of weakness. Again in this disorder, the alteration in the serum potassium level does not adequately explain the profound muscle weakness that may occur.

Hyperkalemic Periodic Paralysis With Myotonia

In 1961, Van Der Meulen and associates[16] described a family who had hyperkalemic periodic paralysis but who had a history of myotonia and, on examination, could be shown to have limited percussion myotonia of the muscles of the tongue and thenar eminence. Significantly, by giving potassium salts, an attack could be precipitated in these patients and a spontaneous attack could be made worse. It therefore became of great importance to establish the kind of periodic paralysis before treatment was begun with potassium salts.

Paramyotonia With Periodic Paralysis

Patients with paramyotonia, as described by Eulenburg[17] in 1886, have paralytic episodes similar in many ways to those experienced by patients with periodic paralysis but different in that the attacks are provoked almost exclusively by exposure to cold. Such patients do not have alterations in serum potassium level, but do have percussion myotonia of the muscles of the tongue and of the thenar eminence. This disorder runs a relatively benign course and usually requires no specific treatment for the myotonic or paralytic symptoms.

A comparison of the clinical features,

pharmacologic effects, electrolyte alterations, and electromyographic changes for the five types of familial periodic paralysis are summarized in Tables 1, 2 and 3.

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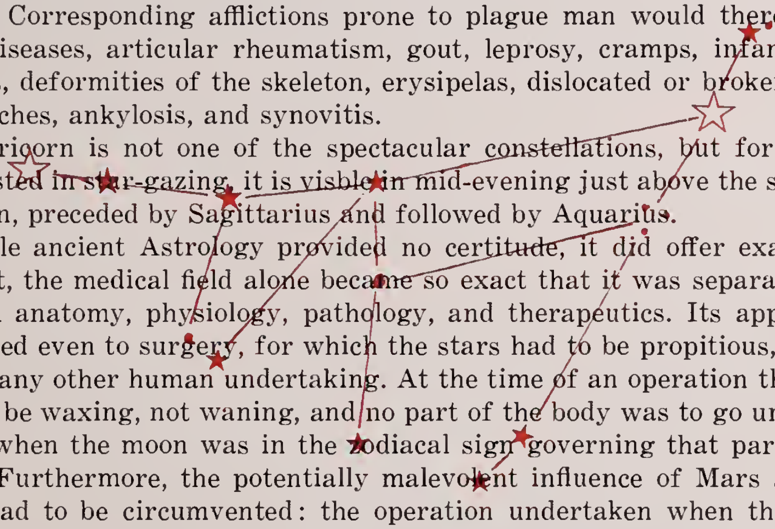
Astrology and Medicine — Capricorn, the Goat

In the early pseudoscience of Astrology the zodiacal sign of Capricorn governed the knees specifically, and, in general, the hair, skin, joints, and bones. Corresponding afflictions prone to plague man would therefore be skin diseases, articular rheumatism, gout, leprosy, cramps, infantile paralysis, deformities of the skeleton, erysipelas, dislocated or broken bones, toothaches, ankylosis, and synovitis.



Capricorn is not one of the spectacular constellations, but for anyone interested in star-gazing, it is visible in mid-evening just above the southern horizon, preceded by Sagittarius and followed by Aquarius.

While ancient Astrology provided no certitude, it did offer exactitude. In fact, the medical field alone became so exact that it was separated into zodical anatomy, physiology, pathology, and therapeutics. Its application extended even to surgery, for which the stars had to be propitious, as well as for any other human undertaking. At the time of an operation the moon had to be waxing, not waning, and no part of the body was to go under the knife when the moon was in the zodiacal sign governing that part of the body. Furthermore, the potentially malevolent influence of Mars and Saturn had to be circumvented: the operation undertaken when those two planets were so positioned in the sky that their baleful influence would be relatively ineffectual.

Ideals are like the stars — we never reach them, but like the mariners of the sea, we chart our course by them.—Carl Schurz

MUNCHAUSEN'S SYNDROME

Munchausen syndrome is a term aptly derived from the fabulous 18th century character, Baron Munchausen, one of the grand raconteurs of all time. His "Singular Adventures" comprise his mock-heroic travels and campaigns in Russia, his amazing adventures at sea, and other incredible enterprises far and wide: an extravaganza based on bold exaggeration, adroit prevarication, and unabashed braggadocio — capitalizing, in short, on the "big lie." Munchausen was fully cognizant that lying is an art; that the magnitude of the lie must be carefully calculated to exploit gullibility to the utmost.

History reveals how dangerous and sinister the "big lie" can be; Hitler's national policy demonstrated the success of the theory that if a lie is big enough, it will stun the mind into acceptance without question or doubt.

In the hands of a literary expert, however, the "big lie" can be a charming and captivating device — as illustrated by Munchausen's story about his greyhound, apparently an ambisexual animal, since for literary expediency, it was either male or female as the occasion required.

"Whilst a greyhound — I must observe she was a bitch — She coursed one day a hare, which appeared to me uncommonly big. I pitied my poor bitch, she was big with pups, yet she would course as fast as ever. I could follow her on horseback only at a great distance. At once I heard a cry as it were of a pack of hounds — but so weak and faint, that I hardly knew what to make of it. Coming up at last, I was greatly surprised. The hare had littered in running; the same had happened to my bitch in coursing — and there were just as many leverets as pups. By instinct the former ran, the latter coursed, and thus, I found myself in possession at once of six hares, and as many dogs, at the end of a course, which had only begun with one."*

By analogy, then, the Munchausen syndrome consists of a plausible pattern of ingenuous and convincing pretense and prevarication, the transparency of which is usually not immediately evident to the doctor whom the patient is deluding. The psychopath with a Munchausen syndrome is capitalizing on the principle of the "big lie."

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*The Singular Adventures of Baron Munchausen by Rudolph Raspe and others, p. 12.

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Shun idleness, it is the rust that attaches itself to the most brilliant metals.—Voltaire

The Doctor's Visit, Jan Steen 1626-1679, Mauritshuis, The Hague

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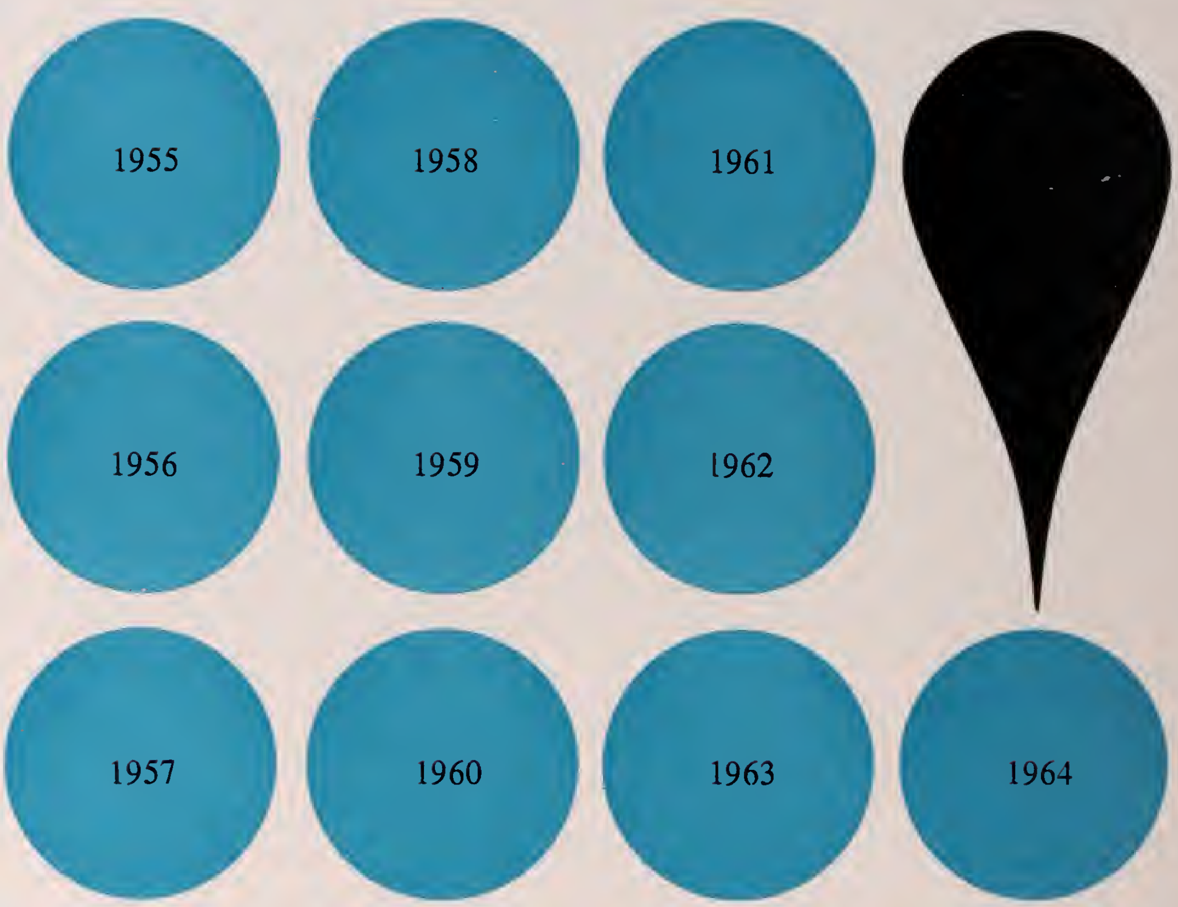
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Editorials

The Mayo Enterprise

A Study in the Anatomy of Success

LIKE A mighty Oak, the Mayo Enterprise has outlived several generations of active participants, continuing to gain strength, vigor and stature with succeeding years. The combination of events and of qualities in individuals that leads to success is not easy to anatomize. Whereas the fortunes of most institutions and nations fluctuate considerably, the Mayo Enterprise continues to go steadily forward. All who visit the capitals of Europe have seen how frequently ostentatious monuments have been erected to commemorate hollow victories. From its earliest beginnings, the eyes of the Mayo Planners have been fixed on the distant horizon. Though venerating the past, their concern has been primarily with the future.

The Mayo Clinic grew quickly from a large and successful General Practice to world-wide distinction as a Surgical Clinic. The Brothers Mayo were probably the first surgeons in the world to insist on a complete physical examination for every patient undergoing surgery. They foresaw the importance and the life-giving effect of research upon the entire activity of the Clinic and its participants long before this development found general acceptance in University Surgical Clinics. Much of the early success of the Mayo Enterprise emanated from a continual striving by the Brothers Mayo to achieve surgical results as good as or better than the best and with lower surgical mortalities. Moreover, an attitude of genuine sympathetic concern for the welfare of the patient has always been patently in evidence.

The Medical Profession has come to look to acceptance of a new therapeutic device by the Mayo Clinic as an indication that the proposal is ready for general adoption. The importance of specialization for achievement was recognized early by the Brothers Mayo. They sought young men of promise who would adapt comfortably and efficiently into the Clinic activities, providing them with unlimited opportunities, deriving as much satisfaction in the accomplishments of their associates as though it were their very own. Life in the home as well as in the Clinic was geared by Drs. Will and Charlie to the precept of sharing, a concept finding ever increasing recognition in the solution of international problems.

Establishment of the Mayo Foundation as an integral part of the Medical Graduate School of the University of Minnesota has been significant in the present important role of the Mayo Clinic and Foundation in providing superior clinical training to large

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numbers of men and women from all parts of the world. The basic wellspring of the continued success of this Great Enterprise is owing to the genius and wisdom of the Brothers Mayo in creating unusual opportunities for graduate training as a corollary of a large, active and highly specialized practice in the broad parameters of medicine by very able representatives, complemented by many well-integrated research programs. The marvel of it all is that only within the past few years, since advent of the largesse of the United States Public Health Service in the support of research, has the Mayo Clinic and Foundation sought outside support for their activities.

Vision, leadership, and prudence have characterized the Mayo Enterprise since its beginnings. The Mayo Centennial serves to emphasize the significant and remarkable world-wide impact of the role of Medicine on the modern scene.

To the entire Mayo Family and their associates, now looking toward a fourth generation participation, every member of our noble profession will welcome the opportunity to say, Well done and may the coming century smile kindly upon this Great Institution so that it will continue to prosper and to serve our Fellowman, the Profession, and the Science of Medicine with even greater distinction and effectiveness in succeeding generations.

Owen H. Wangensteen, M.D.*
Minneapolis, Minnesota

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*From the Department of Surgery, University of Minnesota Medical School, Minneapolis, Minnesota 55455.

"My Brother and I"*

AN HISTORIAN realizes early in his career that the chain of causality is very difficult to forge. The complications of the chemical mechanisms in biology hardly surpass the complications of the social mechanisms through which we establish and maintain the institutions which embody our communal and professional lives. Nothing is easy to explain that is worth explaining. Sometimes the mere sequence of events is difficult to establish. That is why I was interested in this whole congeries of events, distinct but related, which approximately a century ago brought about a change in the situation of Minnesota medicine, with further changes about a half century later.

Something like 120 years ago, there was one doctor, Dr. Christopher Carli, west of Prairie du Chien in the Minnesota Territory. Then something like 111 years ago, a group of enterprising young doctors got together in St. Paul, less than a dozen in number, to establish the Minnesota Medical Society. Seventy-five years ago the Medical School of the University of Minnesota was established, and then fifty years ago the negotiations were begun which led in very short order to rapprochement between the Mayo institutions and the University through the establishment of the Mayo Foundation for Medical Education and Research. About the same time, the University extended the system of full-time appointments in clinical disciplines and set up a program of graduate degrees. These were important, indeed epical, events in Minnesota medicine.

Let me remind you of another event which took place on the 27th of March 1893. This was an event less striking in itself, perhaps, but momentous in its consequences. It was a meeting held in the Ryan Hotel in St. Paul for doctors of Ramsey County, Dr. John F. Fulton presiding, at which cultures of the Cholera Vibrio were demonstrated by Dr. Walter Reed. Dr. Walter Reed's two years in Minnesota have been somewhat neglected by his biographers, but they were, neverthe-

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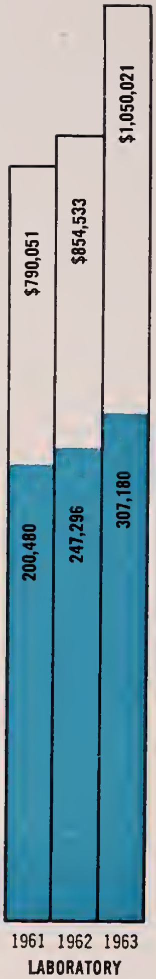
*Précis of Remarks of Lloyd G. Stevenson, M.D. Annual Banquet of Minnesota State Medical Association May 19, 1964.



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less, important. They were important for him, and they were important also for Minnesota medicine. After the meeting, Dr. Reed was introduced to Louis B. Wilson. For some little time thereafter they worked together in the biology laboratory at the St. Paul High School, and they established there the first bacteriological laboratory anywhere in the West.

The practicing doctors who were anxious to widen their horizons, were eager to learn more about this disease, cholera, which had ravaged America from time to time and which was not finished and done with even then. This was close to the end of the 19th century, a century characterized by great outbreaks of gastrointestinal infections. Typhoid was still one of the major problems of medicine everywhere. The Medical School was only five years old at the time; it represented, as a part of the University, the link between the clinical branches of medicine and the basic sciences. But the medical chemistry from which much was hoped, and which in the end was not to disappoint these expectations, had made very little noise in the clinical world since the time approximately fifty years before this when William Worrall Mayo was an instructor in physics and chemistry in the Bellevue Hospital Medical College in New York. Pathology and bacteriology were the sciences of medicine at this time. Bacteriology particularly had to be established and pursued if Minnesota was not to remain backwoods in the national and international medical scene. In 1853, those enterprising young men got together to establish this Association; they met in a court house. These facts are not insignificant. They indicate the limited resources of what was still, in many ways, a frontier society, but they also indicate that community of interest and action which was to transform this society and was to change crude institutions into world centers of medical research and medical education. This was a beginning, when Louis Wilson organized and developed the laboratories of the Mayo Clinic and began to learn, from Walter Reed, the elements of bacteriology.

Sir William Osler used to say that Minerva Medica has a way of moving her temple from time to time, so that it is established now in Leyden, now in Edinburgh, now in Paris, now in Vienna, now in Berlin. I think that the goddess, who moves about very rapidly these days, and who has a rich inheritance so that she can maintain temples in many places at the same time, has never established a temple with such alacrity as she showed in the establishment of her Minnesota sanctuary. The change which took place was a change in medical organization, medical teaching, medical research. It was a change also in the provision for medical care. This change, this development of a team approach, the marshalling of many kinds of skills, of special talents and special training, is one of the great contributions of the Mayo Clinic. It was not uniquely developed here, but it was developed very early, to a high degree, and with great success.

The great contribution of the Mayo Clinic was an organizational one. Fifty years ago, when Dr. W. J. Mayo and his colleagues undertook to reorganize graduate education in clinical branches, what they were doing was providing a measure, a standard, of specialty attainment. This is a job which has been taken over by the National Boards since that time, so that the need for that sort of thing does not exist as it did; but it was then a very real need: this training and recognition of the specialist, of progress toward providing the best care for the patient at many levels and through many disciplines. I know of no other center where this was done so early, in such a systematic way, and with such complete success. This was achieved despite considerable geographical and other difficulties.

In reading these tales about the Mayos with Charles and their father, I was very much struck by two things: one is the spirit which is embodied in the famous expression, "my brother and I"; the other is, how many fights people got into.

A healthy situation is one in which people frankly disagree with each other. Perhaps the stories of the great battles of the Titans are indicative of their strength of purpose as well as of their irreverence.

The strong men were not all on one side

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in these battles. The spirit which prevailed was the spirit of "my brother and I." This is the spirit that informed Dean Lyon, Dean Ford, and President Vincent as well as the Mayo Brothers. It was the spirit of frank disagreement, discussion, accommodation, and continuing conviction. These men held their convictions very firmly; they did not yield them easily. The institution formed by these men not only survived but flourished in an atmosphere of controversy.

It is remarkable that it happened so quickly, for it came about only with stupendous effort, striving, dedication, hard work, and a fair amount of disagreement. Yet the healing influence was always there, the spirit which surmounted not only the outward circumstances and the outward difficulties but which surmounted also the internal disagreements and divergencies of opinion which are bound to exist when intelligent men debate important issues.

I hope that life is not too peaceful in Rochester. I hope that life will not solve all its problems tomorrow; that it will not conclude, when it enters the door of one of these great buildings, that it is walking in any sense on hallowed ground; and that Rochester, St. Paul, Minneapolis — and Minnesota medicine in general — will be marked by that mixture of reverence and irreverence, that mixture of determination and accommodation, which characterized the Brothers Mayo and the representatives of the University, the Association, and the other groups in those battles long ago. That was a wonderful spirit. It was a very happy and fruitful and successful accommodation of differing points of view. It was the spirit of "my brother and I."

Lloyd G. Stevenson, M.D.
Professor, History of Science and Medicine
Yale University

The Doctors Mayo

Their Influence Upon Younger Men

IN THIS Mayo Centennial year I am pleased to have the opportunity to join many others in paying tribute to Dr. Will and Dr. Charlie Mayo, who gave so much of themselves to our community and to the world.

What sort of men were these Mayo brothers? One of their earliest and closest associates, Mr. H. J. Harwick, has described them in this way:*

"The first and perhaps greatest lesson I learned from the Mayos was that of teamwork. For 'My brother and I' was no mere convenient term of reference, but rather the expression of a basic, indivisible philosophy of life.

"The two men complemented each other perfectly. Doctor Will, a natural leader, was rather reserved, analytical, dominating (though without arrogance), relentless in demanding perfection of himself and others, with an uncanny ability to foresee the future. Dr. Charlie was warm, understanding, wonderfully humorous, possessing 'the common touch' in the finest sense of that abused phrase. Often the younger brother would influence Doctor Will toward a less stern approach to a problem. Often, in his turn, the elder brother would influence Doctor Charlie to temper impulsiveness with caution. . . .

"Like all brothers, they sometimes disagreed, and at times their disagreements became rather sharp. Such was the bond of their affection, however, that invariably they found a way to resolve their differences harmoniously. Moreover, agreements far out-

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*Harwick, Harry J.: *Forty-four Years With the Mayo Clinic: 1906-1952.* Whiting Press, Inc. Rochester, Minn. 1957, p. 5.

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numbered disagreements, for it was remarkable how often 'thinking with the head' and 'thinking with the heart' arrived at precisely the same conclusion in analyzing a given situation. . . .

"They made an incomparable team, the Brothers Mayo, and their example influenced us all. Any question as to the respective contributions of the two men would be as unanswerable as it would be irrelevant. It was the combined contributions of the two that mattered, and this would have been a lesser institution without either."

This organization was built by men and women, and our successes and mistakes are those expected of live people with human strength and frailty. But these two men we honor created something new in the field of medicine. Almost nowhere in our country were there any physicians who were working together in private practice for the mutual advantages to patients and themselves. In most areas of our country, medicine centered about universities, largely in big cities, and the pattern often followed the Prussian system of a professional pyramid with the Herr Geheimrat Professor at the top. When he spoke all others listened; he led and they followed. This philosophy persists in many countries today — and in parts of this country — so that the younger man is suppressed and works hard and waits (with varying degrees of patience) until The Professor dies. When I was in medical school, our Professor of Surgery was well into his eighties and another Professor hadn't given a lecture for six years; he had had a stroke and couldn't talk, but he could still breathe, so he was still Professor. And when I interned, the most prominent surgeon had had the same assistant for 10 years, who was permitted no private practice, "because then he wouldn't be an assistant," and who, after these 10 years, was being paid less than the surgeon's nurse anesthetist.

To my knowledge there is not a single instance of voluntary group practice anywhere in Europe; I am, of course, not referring to "group practice" instituted by governments and controlled by them. In this country there are now hundreds of voluntary groups, and the inspiration and planning for such practice began with the Mayos in Rochester. When patients ask, "Why didn't group practice originate in a city, or why didn't the Mayo brothers move from Rochester early in their practice?" I answer by saying I don't believe organized medicine and the medical schools of that day would have permitted them to develop this "revolutionary" or "socialized" brand of practice; the ideas, ideals, and plans of these visionary pioneers would have been strangled by aged hands. And, I repeat, there remain many areas in our country where the old Prussian system remains — often in universities — and where their medical students are discouraged from applying for Fellowships in the Mayo Foundation. When I meet one of these critics, I ask, "Do you have a dime?" He is startled, but usually he produces one. I then cover it with a dollar bill and say, "This dollar against your dime that you've never been in Rochester. You wouldn't pass judgment on a heart without listening to it — or on an abdomen without examining it — but you will pass judgment on us without ever seeing us!" I make a lot of dimes that way — and lose a lot of "friends."

On this Centennial occasion I'm remembering these brothers because I personally am indebted for what they did to make possible a *new* type of medical practice in which all efforts are made to offer the *young* man an opportunity to grow and contribute. We must see to it that no young man is ever prevented from trying new ideas and technics. What little I have done was made possible by the Mayo brothers, the Plummer brothers, Russell Wilder, Samuel Haines — any number of older consultants and friends. And my job now is to do all I can for another generation. I must make sure that no young man will ever say that he was denied an opportunity to grow because I said, "That's my field of interest."

Several years before their death, Dr. Will and Dr. Charlie appeared at a meeting in Plummer Hall on the occasion of their retirement from active participation in all that they had built. They said about as follows:

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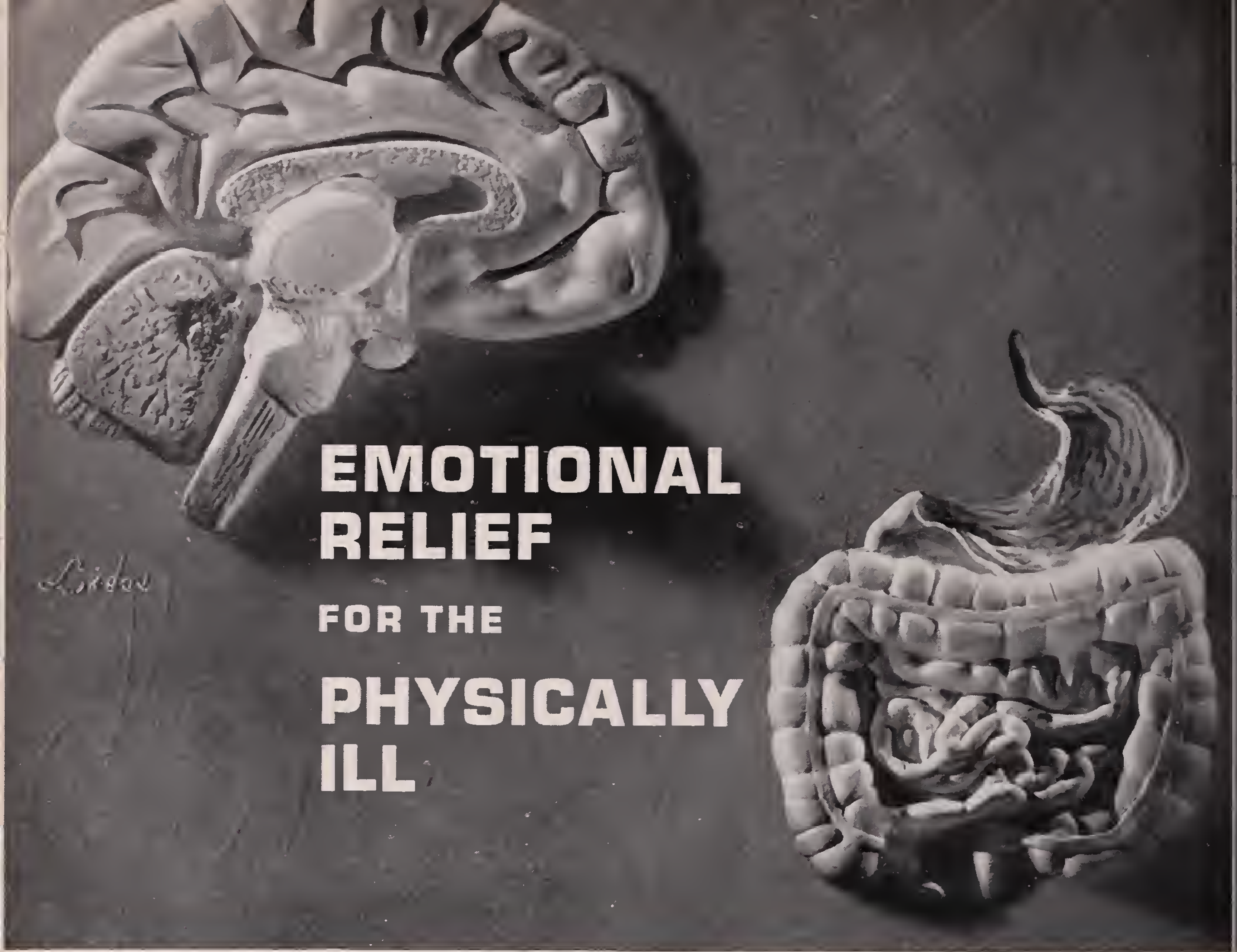

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When the brothers died in 1939, 25 years ago, Dr. Richard M. Hewitt wrote as follows for the records of the Surgical Society: "Those who in years to come peruse these minutes, may justly question what manner of men were we who, experiencing bereavement such as ours in recent months, yet inadequately expressed it. Let them remember, then, that those whose greatness they strive to recreate from graven names and printed pages were living men with whom we walked and talked and laughed: our preceptors, our colleagues, and our friends. We are too close to this grief to describe it: 'True sorrow makes a silence in the heart.'*

"These are the facts which we must record in these minutes: That Charles H. Mayo departed this life on May 26th of this year, William J. Mayo on July 28th. There is left for us their precedent — that immortal part of them — to cherish and hand on.

"Portions of that precedent seem particularly left in trust to us, the surgeons of the institution which our great preceptors founded. They worked for something even greater than themselves, which lies in the future and which must be effected by their successors. Very gradually at first, then more definitely, as old age approached, they withdrew from the affairs of this society and of the Clinic, encouraging their successors to plant their feet firmly in the way. They kept to themselves no knowledge or skill which they could impart to younger men. Always available for consultation and advice, yet they did not assume authority in another surgeon's case. They insisted that each surgeon have a free hand on his own service and that he shoulder the responsibility thereof. Guidance without pampering; help without meddling; these are the principles by which we were trained. Let us train others thereby and, as we close ranks for the months and years ahead, as our great departed mentors would have had us do, let it be said of us: 'They helped every one his neighbour; and every one said to his brother, Be of good courage.' "**

Edward H. Rynearson, M.D.***
Rochester, Minnesota

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*Dr. Hewitt's minutes from Robert Nathan, "A Cedar Box," Sonnet V.

**Isaiah 41:6.

***Section of Medicine, Mayo Clinic.

Chatting with Dr. Charles H. Mayo

Little Things I Remember

(Dr. William J. Mayo and Dr. Charles H. Mayo both died in 1939. During 1964 the Mayo Centennial, commemorating the approximate birth years of the two brothers, will be observed in Rochester. The most important event of the year will be an international symposium held on September 16, 17 and 18 in Rochester on the theme, "Mirror to Man: Man's Adaptation to His Expanding Environment," presenting the views of seven speakers of world repute. In addition, the United States Post Office Department on March 31, 1964, announced that a postage stamp honoring the two Mayo brothers will be issued some time during the year. The following story is presented during the Mayo Centennial year as a reminiscence concerning Dr. Charles H. Mayo by one who knew him well.)

Continued

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Supplied: Bottles of 50 capsules.

1. Dorfman, W., and Johnson, D.: *Overweight Is Curable*, New York, The Macmillan Company, 1948, p. 16.

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IT WAS shortly after 1 o'clock when I met Dr. Charles H. Mayo in the subway under First Street in Rochester, as I was on my way from the Kahler Hotel to the Mayo Clinic. He was limping badly—hardly able to walk. He was not using a cane or any other type of support. I immediately thought that he probably had fallen on the ramp in the subway, just around the corner from the point at which we had met. He smiled as I approached him.

I said, "What in the world is the matter, Dr. Charlie?"

He replied, "I'm walking pretty good now, but you should have seen me 30 minutes ago. I've just come from Mel Henderson's* office. He examined me and said there was nothing wrong with my knee. I went to his office in a wheel chair."

Still smiling, he repeated, as he hobbled away, "I really think I'm walking pretty good now. It just shows the effect of mind over matter."

Some time later, I was examining a middle-aged woman who had come a long distance to see Dr. Charles Mayo. She was intelligent, talkative and nervous. She complained of a gnawing, drawing pain in the lower right abdominal quadrant. Her appendix had been removed some years previously through a right rectus incision. Physical examination and all special studies did not reveal any cause for her complaints. She insisted on seeing Dr. Mayo. I called the late Dr. Joseph G. Mayo, Dr. Charlie's son, who was his first assistant, and told him the story. Joe asked me to bring the patient down to the third floor, to Dr. Charlie's office. Dr. Charlie, at that time, was no longer making floor calls.

Dr. Charlie talked with her as he palpated her abdomen. In a low, mumbling voice, he said, "You know, that old appendix gives many people a lot of trouble."

"But, Dr. Mayo," she interrupted, "I had my appendix removed many years ago."

"Yes, I know," he said, "but you know those old adhesions can pull on the bowel and cause some people a lot of trouble."

"Do you think that could be my trouble?" she again interrupted.

"Yes, adhesions can produce a lot of discomfort in some people," said Dr. Charlie.

"Oh! Thank you, Dr. Mayo, I'm so glad to know my trouble."

When I saw her the next day, I said, "Mrs. S., how do you feel?"

Beaming, she replied, "You know that trouble in my lower abdomen has completely gone. I haven't felt a thing since Dr. Mayo examined me. Isn't Dr. Mayo wonderful?"

Again, as Dr. Charlie had said, "It shows the effect of mind over matter."

Yes, Dr. Charles H. Mayo was wonderful. He walked and talked with the common people; he spoke their language and understood them thoroughly. Like Abraham Lincoln, he was one of them. At the same time he was the most versatile and the most skillful surgeon of his day, a master craftsman in many surgical fields. "He lived abundantly," is the inscription on the foot stone at his grave. It best describes him.

Bayard T. Horton, M.D.**
Rochester, Minnesota

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*Dr. Melvin S. Henderson was head of the Section of Orthopedic Surgery from 1914 to 1938.

**Emeritus Staff Member, Section of Medicine, Mayo Clinic.

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Avoid extremes; forebear resenting injuries so much as you think they deserve.
—Benjamin Franklin

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A Note on Dr. Will Mayo's Way of Getting a Job Done

DR. WILL MAYO had many ways of getting a job done. This is the story of two of them.

In 1931 Dr. Will sent word to me by way of Dr. George E. Brown that he would like to see me in his office at 4:00 p.m. on a certain Monday afternoon. Dr. Brown accompanied me to Dr. Will's office. Mr. H. J. Harwick was there when we arrived. Dr. Will greeted me in a friendly manner and commented briefly on some of the research work that I had done. Then he said, "All of my life, I have been interested in the treatment of cancer. Much has been accomplished, but so much remains to be done. . . . Some time ago I talked with Professor Blair Bell in England, who told me that men and women working in the lead industry for varying periods of time, sometimes became sterile. Some of them remained sterile for several years after leaving the industry. Bell had also noticed that persons with advanced cancer, who had been forced by the exigencies of life to take employment in the lead works, often improved markedly. It occurred to Bell, therefore, that lead had a destructive effect on rapidly growing cells. His observations suggest its possible use in the treatment of cancer." Then he added, "Because of your training and interest in medical research, I hope you will become interested in the treatment of cancer with colloidal lead preparations. I will give you whatever support you need."

As I listened, I took notice of the motto on his desk, "He loved the truth and sought to know it." I thanked Dr. Will, but said, "I would like to think over the problem for a day or two and let you know." Dr. Brown and I then returned to the tenth floor where the new section of vascular diseases was housed. He was the head of the section, and I was a member of it.

The surgical society met that same Monday night, less than three hours after I had left Dr. Will's office. During the meeting (so I was told later), Dr. Will announced that I would begin treating inoperable cancer patients with colloidal lead the following day. At 8:30 the next morning I began to receive phone calls from surgeons saying, "Will you please see so-and-so at St. Marys Hospital or so-and-so at the Colonial Hospital." I tried to explain, but they would not take no for an answer. That afternoon at 1:30 every consulting room at S-10 East was occupied by a patient with inoperable cancer. Dr. Brown threw up his hands, saying, "Something has to be done — the section can't function. . . ." An hour later, Dr. Fred Rankin came to see me. Among other things he said, "You've stolen my thunder." I frankly did not know what he meant. And then he added, "Bargen, Osterberg, and I are treating a few patients who have inoperable cancer with colloidal lead phosphate." I had been totally unaware of it. Pausing for a moment, I said, "Well, Fred, you now have a fourth co-worker." The research work promptly began in earnest. The announcement to the surgical society was never mentioned to me by Dr. Will — ever.

In 1932, we gave our first report on lead treatment for inoperable cancer at the Mayo Clinic Staff Meeting.[1] Dr. Will discussed our report. His comments read in part: "The report given this evening by Osterberg, Horton, Bargen, and Rankin is a careful summary of our experience, given without enthusiasm or pessimism. It is merely an approach to the most important subject before the medical profession today, calling attention to the fact that rapidly growing cells with large nuclei are more vulnerable than other cells, because the nuclei are less protected, and may be poisoned by lead. It is equally evident that other cells of the body are at least temporarily affected by lead, but to a lesser degree. We must bear in mind that only patients whose condition has been hopeless have been subjected to this treatment. . . . We cannot yet estimate the value of lead treatment in cancer, but at least deductive reasoning from the facts may lead scientific imagination to help solve the problem."[2]

Continued

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Years later in 1937 I met Dr. Will in the lobby of St. Marys Hospital on a Wednesday at about 11:15 a.m. as he was leaving for the clinic. I said, "Do you have time to see the results of an interesting study which has just been completed? I think it will interest you." Without hesitating a moment, he said, "Yes, I would like to see it." I hurriedly explained to him that he would have to descend some steep, poorly lighted steps into the basement to a special laboratory that had just been opened. I led the way and he followed. As we walked along, I explained to him that I had gotten the idea that one should be able to make a photographic record of the sounds (vibrations in the tissues) arising from an arteriovenous fistula and also from an aneurysm and thus be able readily to differentiate accurately between the two lesions. Dr. E. J. Baldes had listened to my theory and thought it plausible. After experimenting with a number of pickup units, Dr. Baldes finally came up with a Piezo-electric stethophone. By this method a photographic record of the vibrations in the tissues was obtained. Dr. Baldes was just completing the final duplicate record as Dr. Will and I walked into the little one-room laboratory, the smallest at the Mayo Clinic. The patient being studied was a 32-year-old man with an acquired arteriovenous fistula that involved the right profunda femoral artery and vein. A bruit, which was continuous throughout the cardiac cycle, was heard loud and clear over the amplifying pickup unit. Simultaneously, a photographic record of the vibrations in the tissues was made. For a moment, Dr. Will seemed amazed at the demonstration.

As I walked to the front door of St. Marys Hospital with him, he said, "This is an extremely interesting research project — it is an entirely new idea. Will you be demonstrating it at the Staff Meeting tonight?" And he added, "The Board of Regents of the University of Minnesota is meeting here today and will attend the Staff Meeting." I merely replied, "The program has been completed and was published in the Clinic Bulletin yesterday."

Without additional comments, he got in his car, and was driven to the clinic.

Approximately 30 minutes later, when I was eating lunch at my home, the phone rang. A voice said, "This is Dr. Giffin speaking. I understand you want to give a demonstration at the Staff Meeting tonight. As you know, the program is full and was printed in the Bulletin yesterday." I listened and replied, "Dr. Giffin, I am not interested in appearing on the program tonight. Where did you get the idea?" Dr. Giffin continued, "You can call Mr. H. A. Johnson, and he will arrange to have the equipment, which you and Dr. Baldes are using, transported to the stage in Plummer Hall. You will be the first speaker." And I was. Dr. Will was in the front row with his guests.

The object of our demonstration was to present a new photographic method of recording bruit by which aneurysm and arteriovenous fistula could be accurately differentiated.[3] The bruit that is heard over an aneurysm is recognized clinically as systolic in time. It fades out or becomes inaudible before the next systole, whereas in arteriovenous fistula, the bruit, which is accentuated by each systolic thrust, is continuous throughout the cardiac cycle. However, there are instances in which the clinician has difficulty in making a correct differential diagnosis, and our method of recording bruit is of aid in such cases. The tracings graphically record the difference in the character of the vibrations present in these two types of vascular lesions. We had bridged the gap from biophysics to clinical medicine. The bruit was loud and clear when heard over the amplifying pickup unit — the loudest bruit Plummer Hall had ever heard. Dr. Will congratulated us on our demonstration, but made no comment as to how we got on the program. He had many ways of accomplishing his purpose.

Dr. William J. Mayo was a man of action — a man of great courage — a man of great vision. Go with me to the third floor in the Plummer Building; view, in reverence, his office, which is intact today, as he left it in

Continued

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1939. Read the motto on his desk, and listen while it speaks for the empty chair. "He loved the truth and sought to know it."

The vision of this ideal, which had come to abide with him early in life, was the driving force that motivated his thinking and his doing. Like a pillar of cloud by day and a pillar of fire by night, it guided him throughout his career. This ideal embodies the earnest, upward striving of the soul of a man of genius — not to be subdued, even in death, for it is chiseled on the footstone of his grave.

"He Loved the Truth and Sought to Know It" — lives on. It is the rock foundation on which the Mayo Clinic stands.

Bayard T. Horton, M.D.*
Rochester, Minnesota

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*Emeritus Staff Member, Section of Medicine, Mayo Clinic.

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2. Mayo, W. J.: Discussion. Proc Mayo Clin 7:236, 1932.
3. Horton, B. T., and Baldes, E. J.: A Photographic Method of Recording Bruit: A Means of Differentiating Aneurysm and Arteriovenous Fistula: Preliminary Report. Proc Mayo Clin 12:823, 1937.

The Editor's Soliloquy

Ethics

It is gratifying to note that there are justices who dissent* vigorously from arbitrary adherence to the strict letter of the law in favor of the true spirit of the law, just as there are physicians who sacrifice the commercial aspects of medicine to support the ethics and principals of their profession.

Is there not discernible now an accelerating tendency to exploit legal technicalities, equivocations, loopholes, and evasions — with impunity and without regard for the basic principles of justice? Of ethics? Of integrity? Of the Golden Rule? Do not our mores condone and sometimes even applaud a base policy of self-interest at the expense of the rest of society: our neighbors, our friends, our fellow-men?

If fundamental human and spiritual values continue to decline, it will not be long before our moral common denominator will reach an all-time low — with crass materialism, opportunism, cynicism, philistinism, and atheism prevailing.

To this editor it seems wrong for the courts to allow ethical principles to be abrogated simply because no overt, technical violation of the law can be established.

The great men whom we are honoring in this issue have shown us the way to prosperity without commercialism, success without selfishness, eternal fame without ballyhoo, justice without the law.

Morals cannot be legislated! Nor can man live by law alone!

Carl O. Rice, M.D.

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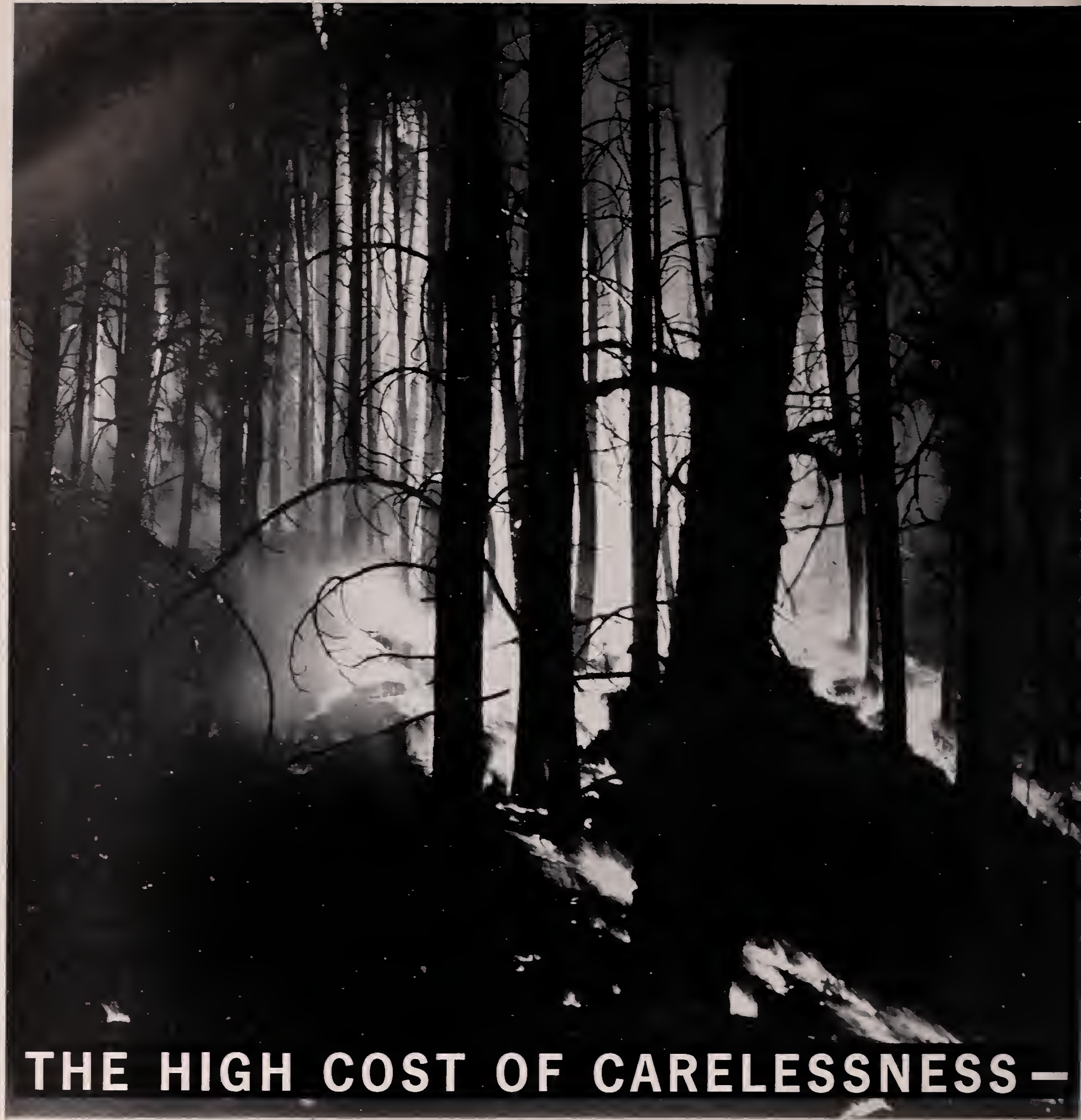
*See Its the Law page 1054.



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Adenomatous Polyps

QUESTION: What is the incidence of carcinoma of the rectum arising in adenomatous polyps?

M.D., Hibbing

ANSWER: If one studies a group of patients with carcinoma of the rectum there will be found an increased incidence in the number of such individuals having adenomatous polyps compared with the incidence of adenomatous polyps occurring in a similar population group not having carcinoma of the rectum. However, it cannot be concluded from this evidence that adenomatous polyps actually serve as precursors to carcinoma of the rectum.

Acute Altitude Sickness

QUESTION: To what pathologic changes are the pulmonary symptoms of acute altitude sickness attributable? Is pulmonary edema a factor?

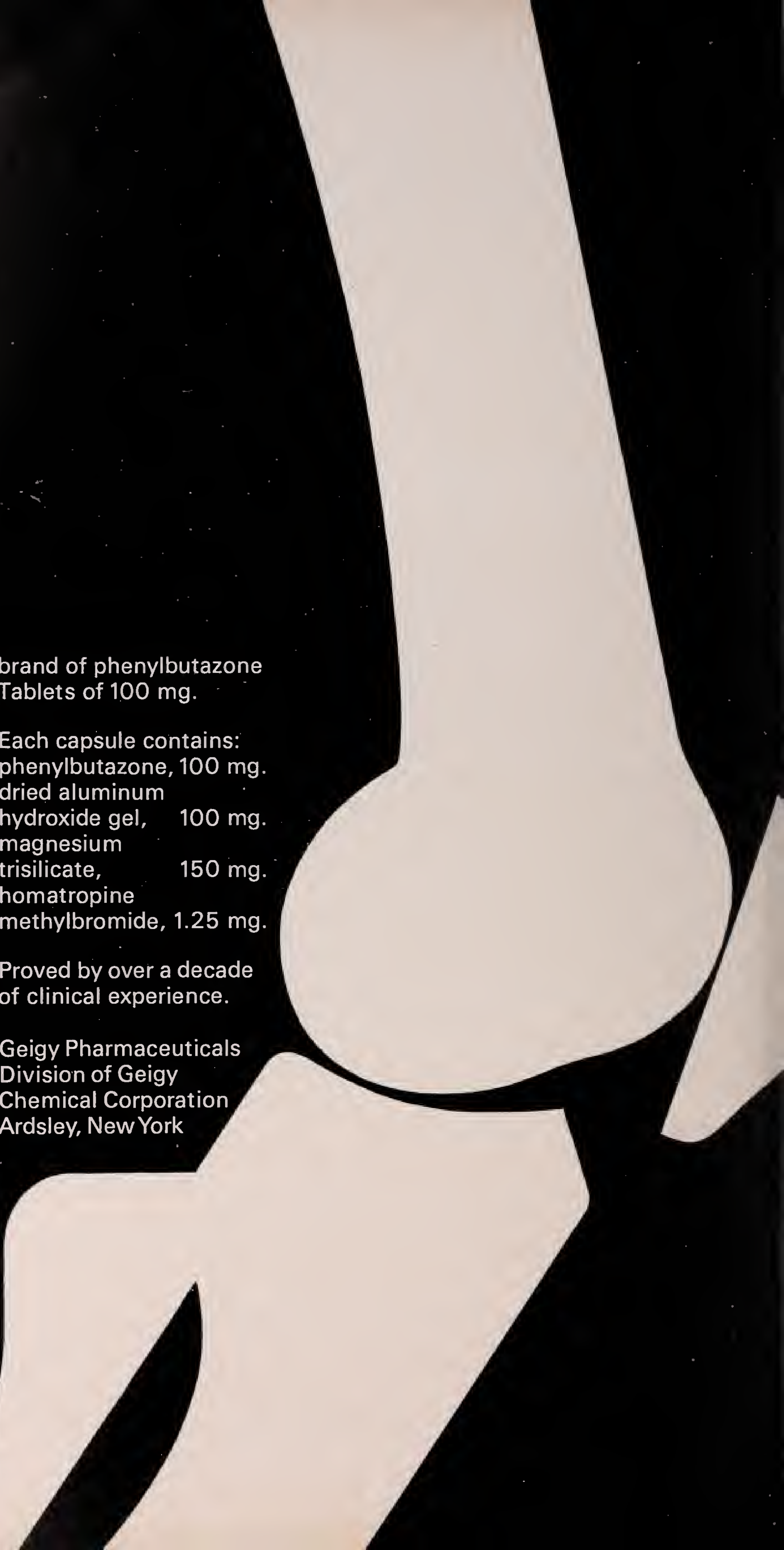
M.D., Albert Lea

ANSWER: Individuals rapidly transported to altitudes over 10,000 feet above sea level develop pulmonary symptoms which are well known. This disease entity is referred to variously as acute altitude sickness, high altitude pulmonary edema, mountain sickness, or soroche. It is generally agreed the symptoms are due to hypoxia. These symptoms may occur even in individuals thoroughly acclimatized to living in high altitudes on returning to mountainous areas, for example, after staying at sea level for one to three weeks.

Pulmonary edema may occur in such patients but the underlying physiopathologic alterations are not clearly established. Acute left ventricular failure or pulmonary venous constriction have been suggested causative factors.

Treatment in such cases consists in removing the patient to a lower elevation, bed rest, and continuous oxygen administration.

The belly will not listen to advice.—Seneca



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Tumor Conference

Complications of the "Enucleation Procedure" For Parotid Gland Tumor

The pitfalls associated with a limited "Enucleation Procedure" for the removal of a parotid gland tumor have been pointed out on many occasions. The wary surgeon knows that in spite of an apparent ready accessibility on clinical examination these lesions often lie beneath the spreading branches of the facial nerve. Removal of such a lesion through a small incision is treacherous, for one or more of the small but important branches of the nerve may inadvertantly be damaged.

Tumor implantation is a second, but no less serious, complication of this type of procedure and is demonstrated by the following remarkable case history.

Case Report

A 56-year-old female was referred to Hennepin County General Hospital because of a recurrent mass in the area of the left parotid gland. She had previously been operated upon and a benign mixed tumor enucleated from that gland. The recurrent tumor at this time extended from just anterior to the tragus down to the angle of the mandible. There were several tumor nodules in the post-auricular area over the mastoid process.

At surgery it was necessary to sacrifice the mandibular branch of the facial nerve because it was intimately associated with the tumor. There were 12 areas of recurrence in the specimen, which included the overlying skin and the remainder of the superficial lobe.

In September of 1957 she was readmitted with several recurrent nodules anterior to the ear. These were removed and the upper two divisions of the facial nerve again could be spared. Two years later several more nodules appeared, necessitating removal. At this time in order to remove the tumor the upper two branches of the nerve had to be sacrificed. Again, in June 1961 nodules reappeared requiring further resection. At this time no thought was given to sparing nerve tissue, for her paralysis was already complete.

At the time of her most recent appearance in the Tumor Clinic and at a time when a fascial sling was proposed for the left side of her face a nodule was found to be present in the incision under the angle of the jaw.

Continued

This patient has had four major operative procedures for recurrent tumor; she has a facial nerve paralysis and she still has tumor present in her neck following the enucleation procedure. At no time has the histological diagnosis been anything but benign mixed tumor.

Benign

Mixed tumors and Warthin's tumors (cystadenoma lymphomatosum) are known to recur if improperly removed. These tumors are less likely to recur if removed with surrounding normal gland tissue in the performance of a superficial lobectomy. If the tumor should lie in the deep lobe, the nerve should be carefully mobilized and the deep lobe removed.

Malignant

Although malignant parotid tumors are less commonly encountered, they do occur. A limited procedure excising such a lesion might spread cancer cells throughout the wound and the chance for a potential cure be lost forever.

The surgeon who undertakes a superficial parotidectomy for all parotid lesions will have optimal results in so far as curing the tumor is concerned. He must, however, accept the fact that he may have a certain number of patients that will develop a temporary facial palsy; and he may, on occasion, perform a parotidectomy for a lymph node which is either in the gland or closely adherent to it.

Experience with patients suffering from uncontrolled malignancies of the parotid or recurrences of benign tumors as described in this case makes the surgeon willing to risk the relatively minor complications involved and to take the added time required to meticulously dissect out the superficial lobe of the gland.

Harrison H. Farley, M.D.
Minneapolis, Minnesota

Primitive Skin Clip

In India and Algeria, fighting ants have been used to hold the edges of wounds together, identical to the manner in which skin clips are used in this day. The jaws of the ants are widely opened, the edges of the wound are held together with one hand while the ant is held with the other, and as the insect is gradually brought near the wound it seizes both edges, holding them. The surgeon then snips off the bodies of the ants and the heads remain until the wound is healed. Andrews: *Nature's Ways.*

How is it possible to expect mankind to take advice when they will not so much as take warning?—Swift

Clinical Path Conference

Clinical Case Presentation

October 2, 1963

A 31-year-old utility service manager was admitted to St. Marys Hospital on April 27, 1963, complaining of headache of four days' duration.

The patient had awakened feeling well on April 22, 1963. About 11:00 a.m. he became aware of a slight tingling of his left hand and of the left side of his face and lips. This persisted for about five minutes. It was followed by a throbbing, bifrontal headache which gradually reached a peak in about one and one-half hours. He was nauseated but did not vomit. During the onset of this headache he noticed that all objects seemed out of focus, but he had no scotomata and no diplopia. He was light-headed, but he experienced no vertigo. He took to his bed, and the doctor was called. The doctor arrived about one and one-half hours after the onset of the headache. He examined the patient, gave him an injection, and had him admitted to a local hospital. The headache began to improve about 45 minutes after the injection, and the patient slept well that night. The next day, a lumbar puncture, done with the patient in the lateral decubitus position, was reported to show an opening cerebrospinal-fluid pressure of 280 mm. of water and a closing pressure of 190. The fluid was clear. There was one neutrophil per cubic millimeter, and the protein content measured 24 mg. per 100 ml. A roentgenogram of the skull and an electroencephalogram were reported as normal. The patient had no headache after the lumbar puncture and was discharged from the hospital on April 24, having been free of headache for three days.

About 7:00 on the evening of April 25, 1963, the patient had napped for a few minutes and awoke with a throbbing headache in the left frontal area. Within an hour this headache became moderately severe but did not reach the intensity of the first headache. However, the doctor was called, and he again administered an injection. About 20 minutes after the injection, the patient suddenly vomited. He was not nauseated. The headache subsided after about two hours.

The patient had had mild headaches in the morning for about two years.

Continued

These headaches had been noticed when he shook his head or stooped over, and he believed that they were related to tension, at least in part. His wife said he had been working under unusual stress during the preceding few months.

In January of 1960, the patient had had abdominal pain suggestive of a duodenal ulcer. An episode of hematemesis had occurred, and treatment with a strict ulcer diet had been continued for six months with good results. The patient's weight increased from 180 to 230 pounds during treatment. Medical history was otherwise not significant.

General physical examination on admission revealed only that the patient was moderately obese. Neurologic examination revealed a slight difference in the knee and ankle jerks, these being more brisk on the left side. One examiner noted that the patient did arithmetic poorly. Funduscopic examination revealed normal conditions. Roentgenograms of the head and chest were interpreted as normal. Results of routine laboratory studies were within normal limits. A radioactive PVP brain scan was performed on April 30, 1963, and no abnormal accumulation of radioactivity was demonstrated.

The patient had little headache during his hospital stay. He was dismissed on May 1, 1963, with instructions for a 1200-calorie, liberal ulcer diet. He was given a prescription for a well-known proprietary headache remedy.

When he was readmitted on May 22, 1963, the patient's wife said that he had been well and comfortable for a few days after his discharge from St. Marys Hospital but that he then began to complain of moderate, generalized headache and that he underwent a marked change in behavior. He had no interest in returning to work and felt that he was being unfairly treated by his employer. He brooded over his failures and felt that he had disappointed his parents. He refused to eat and actually threw his dishes to the floor on several occasions. He used profane language to a greater degree than ever before. When he walked in the yard, his wife saw him stumble into obstacles which he apparently did not see. He became so despondent and confused that he was admitted, on May 11, to the psychiatric ward of his local hospital where an extensive psychiatric examination was done. The referring psychiatrist reported that the patient was oriented but showed gross defects in judgment and insight. There was evidence of confusion, ambivalence, regression, and impairment of intellectual capacity. He became increasingly confused under observation. A single electroconvulsive treatment was administered about May 17. After this treatment, the patient seemed to be more agitated and confused. He had an equivocal Babinski sign on the right side; and, on May 21, he reportedly had "a period of collapse without syncope." On the same day, a pneumoencephalogram was attempted, but the examination was unsatisfactory. That evening the patient was observed to have a "right lid lag." Spinal-fluid pressure in the vertical position was reported to have been 440 mm. of water with a final pressure of 370 mm. of water. The spinal fluid was clear, and it contained four red cells per cubic milliliter and 18 mg. of protein per 100 ml. Medications included promazine (Sparine), 50 mg. four times a day; a combination of dextro propoxyphene, 65 mg., with an APC compound (Darvon Compound-65), one capsule every four hours as needed; and ethchlorvynol (Placidyl), 400 mg. at bedtime. The patient was then referred to St. Marys Hospital for further examination.

On admission the patient was co-operative, euphoric, and confused. He did not know the exact date or his exact location, but he seemed to recognize the previous examiners. There was no evidence of aphasia. He veered toward the right on tandem gait. He fell backward from the sitting or standing position. There was a moderate ptosis and minimal weakness of other facial muscles on the right side. Extraocular movements were normal, but a moderate, rapid nystagmus was present on right lateral gaze. The pupils were small and their reactions were normal. Visual fields were full, and results of funduscopic examination were normal. There was no muscle weakness. There was a slight slowing of finger wiggle on the right side. Co-ordination was recorded as normal, but slow. Stretch reflexes were normal to hypoactive and symmetric. There was a positive Babinski sign on the right side.

The patient was observed on the closed psychiatric ward for three days. At the end of that time, findings on neurologic examination had returned virtually to normal, although the confusion and marked loss of recent memory persisted. Further studies were done.

Discussion

Doctor Greer

Before Doctor Galbraith begins his discussion, are there any questions about the protocol?

Doctor Thomas

No.

Doctor Galbraith

No questions.

In summary, we are presented with a problem of headache and dementia.

Vascular Headache

There are several points in this patient's history which could be explained on the basis of vascular headache. The typical vascular headache of migraine type is of a throbbing nature; it generally is unilateral at onset, but it may be bilateral and is occasionally generalized. This patient manifested all three types of onset on three separate occasions. The prodromata of vascular headache are many and common and are the result of focal vasoconstrictive changes in the brain. In most instances they are visual in nature, such as flashing bright lights, stars, or scotomata. This patient had none of these, but other preheadache phenomena less commonly noted are vertigo, aphasia, confusion, and unilateral paresthesia or weakness in the face or extremities. This patient experienced the symptom of paresthesia for five minutes preceding the first headache and was confused with his third headache. The accompanying symptoms commonly seen with the vascular headache were noted in this patient. These include anorexia, nausea, irritability, impaired memory and concentration, light-headedness, and blurred vision. Personality features and life

Continued

situations, which are important in migraine, were also seen in this patient. These individuals are commonly insecure; they seek to deal with this feeling by becoming inflexible, overly conscientious, meticulous, and perfectionistic. This commonly leads to frustration, resentment, and dissatisfaction with their personal status and with the behavior of those about them. Perhaps as a result of the increasing tension and frustration that this patient experienced in his work he may have suddenly reached the breaking point and plunged into the psychiatric state in which he eventually ended up.

It is certainly true that on occasion patients with migraine headache may have a persistence of confusion, paresthesia, paresis, or other focal neurologic deficit which may take several days to clear; but this is unusual, and I would be reluctant to explain all of this patient's symptoms on that basis alone.

Vascular Anomaly or Intracranial Aneurysm

Vascular anomalies may occur at any site in the brain but are most common in the cerebral and cerebellar hemispheres. When they are large, they may extend from the cortex down to the ventricular surface. The clinical picture usually takes the form of a convulsive seizure, subarachnoid hemorrhage, or both. Commonly, the patient is under the age of 25 when his symptoms appear, but the onset may be delayed until later years. The seizures usually are focal and as a rule are followed by a temporary postictal paralysis or some other neurologic deficit. Headaches associated with angiomata usually are similar to those seen in migraine and may have the accompanying aura. However, the lack of a history of convulsive disorder and the fact that we have no clinical or diagnostic evidence that the patient had a subarachnoid hemorrhage makes this diagnosis unlikely. Intracranial aneurysms — 85 per cent of which involve the anterior portion of the circle of Willis — are common in this age group. They usually are silent and rarely cause headache prior to rupture. If they are large enough, they may produce focal neurologic signs by compression of various cranial nerves. Once again, the lack of a clinical picture simulating subarachnoid hemorrhage and the lack of bloody spinal fluid, even though the spinal fluid was under increased pressure on one occasion, also make this diagnosis unlikely.

Expanding Intracranial Mass

Under this heading I include any expanding intracranial mass, be it tumor, abscess, or hematoma, since the mechanism and the clinical features of headache are like those of brain tumor. Headache associated with an expanding intracranial lesion is produced mainly by encroachment on pain-sensitive structures within the cranial cavity. The headache accompanying a brain tumor usually has a gradual onset, does not throb, and is intermittent. It generally becomes progressively more frequent and severe with the passage of time. It may interfere with sleep, and sometimes it is precipitated, or aggravated, by coughing, straining, or brisk movements of the head. However, there is no clinical feature of such a headache which would definitely indicate that a space-occupying intracranial lesion is present. Other symptoms and signs are essential to making the diagnosis. Of particular importance in the present case was the absence of fever, leukocytosis, and any history of recent infection, either of which would have indicated that the patient might have had an abscess. In addition, we have no clinical evidence of trauma to suggest the possibility of subdural hematoma, although in some cases there is no history of antecedent trauma. Confusion, inappropriate behavior, and other psychiatric phenomena, as well as focal neurologic deficits, do occur in these patients. So the diagnosis of subdural hematoma cannot be completely ruled out at this stage of the discussion. Similarly, tumors of the frontal lobe, or tumors elsewhere that compress the frontal lobes could certainly mimic the findings in this patient without producing notable evidence of increased intracranial pressure. This patient's symptoms of euphoria, confusion, lack of interest, depression, and decreased intellectual function are certainly seen in lesions of the frontal and temporal lobes, and as a matter of fact may result from lesions almost anywhere in the brain. The normal electroencephalogram and skull roentgenograms plus a negative brain scan on the first admission are certainly helpful, but do not rule out a brain tumor in this patient.

Colloid Cysts or Tumors of the Choroid Plexus

Colloid cysts and tumors of the choroid plexus are fairly commonly seen at the necropsy table, but it is exceedingly rare for them to cause any symptoms. Nevertheless, this type of tumor could certainly have caused this patient's symptoms and clinical course. Colloid cysts usually are located in the anterior part of the third ventricle, where they tend to occlude the flow of cerebrospinal fluid through the foramen of Monro. Papillomata arise from the choroid plexus, usually in the fourth ventricle or in the lateral ventricles, and they may produce a similar type of picture. The clinical pictures that these tumors give depend on the production of internal obstructive hydrocephalus with resulting increased intracranial pressure and compression of the surrounding brain tissue. They may present evidence of a focal neurologic deficit, such as was seen in this patient, and commonly patients who have such tumors will present with a rapidly progressing organic dementia, often with sudden coma, and with a rapid deterioration resulting in death. Such patients will not uncommonly complain of headaches which are precipitated by bending, stooping, or shaking of the head. It has been said that these tumors act like a ball valve, causing intermittent obstruction of the foramen of Monro with secondary internal hydrocephalus.

Metabolic or Toxic Disorders

In the final category, metabolic disorders need to be mentioned, although we have no evidence to suggest that the patient had a drug toxicity or any systemic disease involving the liver, kidneys, heart, or mesenchymal tissues, that might mimic this type of situation.

Summary

I am not certain what this patient's condition represents. I suppose a reasonable diagnosis would be that of a combination of vascular headache of migraine type followed by acute, undifferentiated schizophrenia. However, my choice for final diagnosis is a colloid cyst of the third ventricle

Continued

producing intermittent ventricular obstruction which resulted in the clinical picture of a temporary focal neurologic deficit and organic dementia.

Doctor Greer

Thank you, Doctor Galbraith. Doctor Thomas, we would be pleased to have your comments.

Doctor Thomas

Since Doctor Galbraith has presented a detailed survey of the differential diagnosis, I shall touch only briefly on the highlights of this case. First of all we should note that there was a past history of two years of headache, headache whose quality was disquieting. It occurred early in the morning and was precipitated by movement of the head and by postural changes of the body. While such factors may occasionally occur in benign headaches such as those of the tension variety, they are distinctly unusual and should raise our suspicion of the possible presence of a structural intracranial lesion.

Benign Headache

Concerning the present history, the symptom complex which occurred on April 22 was not specific enough to permit a definite diagnosis. As an isolated occurrence it could have been compatible with a vasodilating headache preceded by a vasospastic phenomenon. However, in the light of the past history caution should be exercised. The home physician elected to do a spinal fluid examination which was found to be normal except for an opening pressure of 280 mm. of water. I have no way of knowing whether such value represented truly increased intracranial pressure or was due to insufficient relaxation of the patient. An electroencephalogram and roentgenograms of the skull, performed at a hospital near the patient's home, were also found to be normal. Subsequent examination of the patient here at the Mayo Clinic did not add anything significant, and the man was dismissed on a program of treatment for his headache. I presume, if I had been the consulting neurologist then, I would have handled this problem similarly.

Intracranial Lesion

A short time later, however, the case lost its seemingly benign flavor. The patient began to display marked alteration of behavior and, of most concern, this alteration was a rapidly progressive one leading to quite profound changes within a matter of three weeks or so. Significant may be the note in the protocol that initially there seemed to have been a disturbance of mood as well as of judgment and insight, while the intellect appeared to be less involved. Such a sequence of events is always suspicious, I think, of a frontal-lobe lesion. The neurologically uninitiated, when seeing a patient with intellectual dysfunction, tend to place him automatically into the frontal-lobe category. It should be remembered, however, that there are other regions of the brain which, at least as often as the frontal lobe, give rise to disturbance of intellect. In fact, if the predominant finding were a disturbance of intellect, with preservation of the personality otherwise, I would tend to place the lesion posterior to the frontal lobe. Vice versa, if the changes relatively spare the patient's knowledge of facts, that is, his intellect, and rather affect his ability to do something with those facts; that is, if they impair judgment and insight, as in this case, then I would consider the frontal lobes to be involved. I readily agree, of course, that with extensive lesions of the frontal lobe, especially if the corpus callosum is affected as well, or if the lesion involves both frontal lobes, intellectual deterioration may be profound, but in such cases other personality changes are almost invariably associated.

Getting back to our patient, the mental changes which had developed prompted readmission to the home hospital where a pneumoencephalogram was attempted but was unsuccessful. Whether this implies that not enough air entered the ventricular system for its satisfactory delineation or whether difficulty was encountered in entering the subarachnoid space, I don't know.

Frontal Lobe Involvement

When the patient came to us again a short time later, examination revealed that he was confused and euphoric, findings which could be explained by severe frontal lobe involvement from within or without. Tandem gait was characterized by veering to the right, there was a tendency to fall backwards on standing and sitting, and nystagmus on gaze to one side was demonstrable. I am reluctant to commit myself as to the origin of these signs in this case, for they can be associated with lesions in the posterior fossa, with increased intracranial pressure, or with lesions of the frontal lobes. Gerstmann[1] and others[2,3] have drawn attention to the symptom of retropulsion and to the tendencies of patients with frontal-lobe lesions to fall, explaining these symptoms vaguely on the basis of disturbed tonus from imbalance between frontal lobe and cerebellum. Whether or not frontal-lobe nystagmus exists is controversial and will not be discussed further here. Be that as it may, the frontal lobes are the most likely site of the lesion in this case, and I should like to explain the facial weakness which was present in this patient on this same basis. The occurrence of facial weakness in the absence of weakness of an extremity is well known to occur in patients who have lesions of the frontal lobe; it has been conveniently explained by the close proximity of the anteriorly slanted lower part of the precentral gyrus to the rest of the frontal lobe.

Summary

I would think on the basis of the limited information available that this patient harbors a pathologic process in or around the frontal lobes, the lesion being most likely space-consuming in type, such as a primary or secondary cerebral tumor, an abscess, or a subdural hematoma. For further defense of such a diagnosis, however, I would need to know results of laboratory studies including the status of kidney and liver function.

Doctor Greer

Results of examinations of the urine, including the specific gravity, were within normal limits on both admissions. Determination of blood urea on the second admission gave a result of 24 mg. per 100 ml. The renal status

Continued

was not investigated further. Serum bilirubin was reported to be normal on the second admission.

Doctor Galbraith

Were there any electroencephalographic findings?

Doctor Greer

An electroencephalogram was made on May 24, 1963 (Fig. 1). It was reported to show minimal alpha activity; this was symmetrical but occurred only briefly after the patient closed his eyes. There was a predominant background frequency of six cycles per second, which was approximately symmetrical on the two sides. The record showed a good deal of intermittent, moderate amplitude, bilaterally synchronous, sinusoidal activity ranging from three to five cycles per second. Although widespread, this activity was maximal anteriorly. It was inhibited by alerting the patient but was reconstituted during hyperventilation.

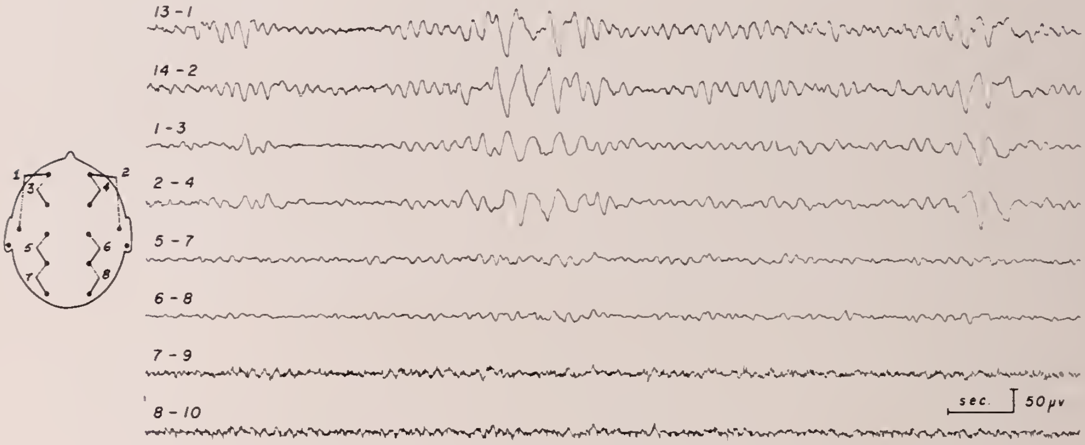

Fig. 1 — Preoperative electroencephalogram shows projected dysrhythmia.

Doctor Galbraith

These abnormalities are the sort that I would expect to see projected from a deeply situated lesion near the midline.

Doctor Greer

Your impression agrees with the electroencephalographer's diagnosis. The EEG diagnosis was "dysrhythmia, grade 2, generalized, maximal anterior." He remarked that these were the changes of a projected variety, as might result from a disturbance deeply situated although similar changes might be seen as the result of heavy sedation. Doctor Galbraith, could you suggest the next step toward making a diagnosis?

Doctor Galbraith

In keeping with my first diagnosis, I think it would be useful to visualize the structures in the third ventricle. A pneumoencephalogram would be the next step.

Doctor Greer

A pneumoencephalogram was indeed performed. Would you like to examine the films?

Doctor Thomas

May we see the plain roentgenograms of the skull first?

Doctor Greer

Yes, sir. These skull films were taken during the first admission in April and were reported as negative.

Doctor Thomas

Thank you. The fractional pneumoencephalogram shows that the entire ventricular system fills easily and is greatly dilated throughout. In the initial upright lateral film (Fig. 2) there seems to be a mass in the third ventricle, anteriorly.

Doctor Greer

Doctor Galbraith, do you think these films are consistent with your original diagnosis?

Doctor Galbraith

Yes, I think so. This mass does not seem to be exactly in the midline. It is more prominent on the left side.

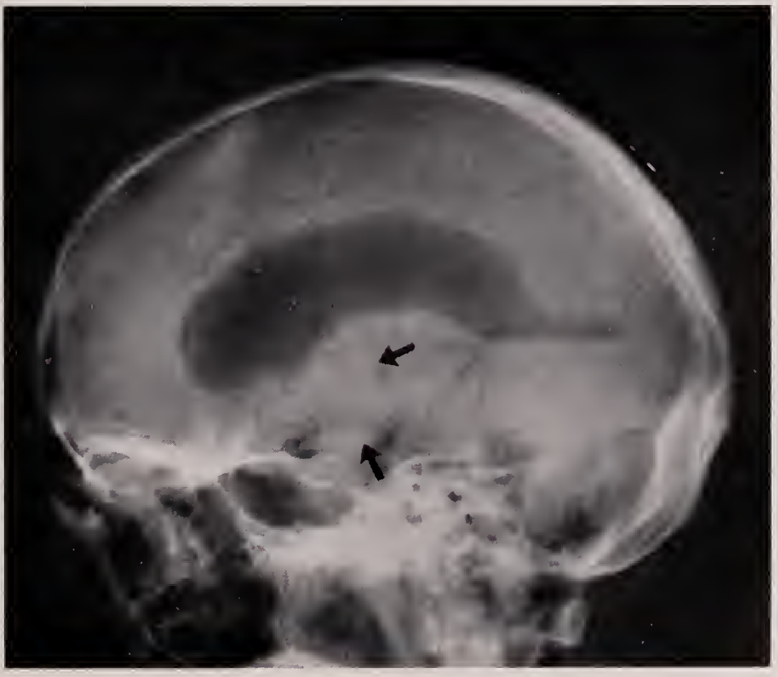

Fig. 2 — Fractional pneumoencephalogram shows dilation of ventricular system and suggests presence of mass in third ventricle, anteriorly.

Continued

Doctor Greer

This study was interpreted to show "mass in the anterior third ventricle, which partially obstructs the foramina of Monro but to a greater degree on the left side. There is dilation of the entire ventricular system. Consider colloid cyst."

Doctor Galbraith

Was the spinal fluid examined?

Doctor Greer

Spinal fluid was obtained at the time of the pneumoencephalogram. The pressure was not measured. The fluid contained 118 lymphocytes and 10 polymorphonuclear granulocytes per cubic millimeter. Protein measured 46 mg. per 100 ml., and sugar, 45 mg. per 100 ml. The concentration of chlorides was normal.

Doctor Thomas

The patient had had a previous pneumoencephalogram only a week earlier. The pleocytosis in the CSF might be attributed, at least in part, to the previous study.

Doctor Greer

Are there any further suggestions about the order of procedure?

Pathologic Findings

Doctor Galbraith

I think we should proceed with the operation.

Doctor Greer

The operation was performed two days later through a right frontal craniotomy, and the right lateral ventricle was entered. The surgeon reported that a mass presented in the third ventricle and that it contained yellow material, but he commented that it was not the grumous material usually seen in a colloid cyst. Some of this material and part of the capsule were sent for pathologic examination. Doctor Sayre has kindly reviewed this case for us and will describe the nature and significance of the pathologic specimen.

The Gross Pathology

Doctor Sayre

The surgical specimen proved to be a craniopharyngioma. This is a tumor which is also known as adamantinoma, Rathke's pouch tumor, and tumor of the hypophysial duct. These tumors are derived from the pars infundibularis of the pituitary gland, according to current thinking. Grossly, they may be suprasellar, invaginating or invading the third ventricle, lying between the optic chiasm and the mammillary bodies, and surrounded by the circle of Willis. Occasionally they may be intrasellar, in which case there is considerable compression of the pituitary gland and associated ballooning of the sella turcica. Probably more frequently there are suprasellar portions and intrasellar portions. The tumors are usually cystic with a rather firm capsule which often glistens and may have various colors, depending on the contents of the cyst. The contents frequently are oily and characteristically contain numerous shimmering cholesterol crystals. Surgeons describe the contents as having the appearance of old motor oil.

Because of the tumor's proximity to the optic chiasm and the circle of Willis, the anterior cerebral-anterior communicating artery complex is frequently stretched so that it compresses the optic chiasm. This results in deformation and notching of the optic nerves or chiasm or both and in various ophthalmologic findings. In a review of 100 cases, Love and Marshall[4] found that the principal portion of the tumor was suprasellar in 33 cases and that the pituitary gland was invaded or compressed in 26 cases. Calcification was evident on roentgen-ray examination in 56 per cent of the cases and on histologic examination in 77 per cent.

The greatest enlargement of these tumors is upward into the third ventricle. From there it may spread widely into the surrounding tissues. As the tumor increases in size, it may occlude one or the other or both foramina of Monro, leading to unilateral or bilateral hydrocephalus. The size of the tumor has no particular relationship to whether the tumor will be mostly solid or cystic. Once the tumor has been surgically explored, and occasionally without operation, there is a possibility of leakage of the cholesterol contents from the cystic portion of the tumor into the subarachnoid or ventricular spaces where apparently the material produces a foreign-body reaction. This reaction may be minimal and produce little alteration in the fluid pathways, or it may be extensive, producing marked interference with the mechanism for absorption of spinal fluid.

Microscopic Pathology

Doctor Sayre

The histologic appearance of these tumors is classic. They consist of cells which have the general appearance of epithelial cells and which occur in sheets or nests of irregular formation. Characteristic is the appearance of the most peripheral cells which are lined up perpendicular to the surface as cylindrical cells with their outermost portions being attached to a thin layer of connective tissue. Just within these palisaded cells is a mass of more stellate or pavement-type epithelium with central nuclei and rather star-shaped cytoplasm. The amount of cytoplasm relative to nucleus varies from area to area. Between individual cells intracellular bridges can be seen, but keratin hyaline granules, as seen in true squamous epithelial cells, are not found. A degeneration frequently occurs in these epithelial cells. This consists at first of a fine vacuolar degeneration which, as the vacuoles expand, gradually results in ballooning of the cells and finally in a breakdown of the cytoplasm and nucleus. As this breakdown progresses, first microcysts and then macrocysts are formed.

Secondary Reactions

Reactions to these tumors occur as a progressive gliotic proliferation. This gliosis occurs around progressing outpouchings of the central tumor, as well as around what is essentially the spilled contents of the tumor or degenerative products occurring within the tumor. These degenerative products consist of cholesterol which is seen histologically as cholesterol clefts, masses of hyalinized material, and foci of calcification.

Continued

Because of the close proximity of these tumors to the hypothalamus, various abnormalities are produced by alterations in endocrine activities on the basis of changes in both the hypothalamus and the pituitary gland. These alterations will vary, depending on the age of the patient when the symptoms of tumor first become manifest. More than 50 per cent of adamantinomas have been found in patients in the first two decades of life. Iyer[5] reported the occurrence of such a tumor in a newborn child, and Love and Marshall[4] observed adamantinomas in patients three years of age. Among patients more than 20 years old, the tumors have been found to be fairly evenly distributed in various ages through the age of 67.

The origin of these tumors has been subject to considerable discussion. There had been noted as early as the middle of the last century that, in the pars infundibularis of the pituitary gland, nests of epithelial-like cells may be found in about 60 per cent of pituitary stalks from patients more than 20 years of age. Subsequent studies have confirmed these findings. A corollary finding of some considerable interest is that such cells are rarely found in patients less than 20. The appearance of these nests is similar, in all major respects, to the appearance of the classic tumor, except for their minute size and the absence of reaction around them. Because of the frequency of their occurrence, it has been suggested that they represent normal alterations associated with aging of the glandular cells of the pars infundibularis. The contradiction in finding the greatest number of tumors in patients who are less than 20 years of age and in the absence of "normal" cell nests in normal pituitary glands from patients less than 20 has been explained by the fact that the tumor influence has acted on the basic substrate, from which the normal cell nests arise, at an earlier age and at a greater degree of intensity. Previous studies[6] have suggested that these tumors arise from remnants of the Rathke pouch which is a portion of the upward invagination of the foregut. It is generally believed, however, that Rathke's pouch is represented only by a slitlike cavity between the pars anterior and the pars intermedia of the gland, that this cavity is lined by columnar or ciliated epithelium, and that this cleft, although it may rarely form a cyst which may be clinically significant, is quite different in all other respects from the classic tumor of the adamantinoma type.

Doctor Greer

Thank you, Doctor Sayre. You have raised several points about this case which deserve comment. To begin with, this tumor was located above the sella turcica and this man had no clinical evidence of endocrine dysfunction, although he was moderately overweight. There were no visual field defects on confrontation, before operation, but tangent-screen perimetry was not performed. Several months after operation, a large temporal scotoma in the right eye was demonstrated on the tangent screen and was presumably due to damage to the right optic nerve. The original roentgenogram of the skull was interpreted as negative, but in retrospect a very faint line of calcification is evident above the sella turcica on the original films.

Most of the tumor, which measured about 3 by 4 by 4 cm., was removed surgically. The deepest part of the sac could not be freed and was coagulated as thoroughly as possible. The patient's postoperative course was reasonably smooth, considering the critical area of surgery. He had received a cortisone preparation before operation, and this was gradually tapered off over a period of about two weeks. In the first few postoperative days, he had considerable diuresis, but he never developed frank diabetes insipidus.

Radioactive cobalt therapy was instituted about two weeks after operation and was continued for a month, to a total dose of about 6000 roentgens through bi-temporal ports.

The patient has remained confused and disoriented, although his wife reports his gradual improvement. He was readmitted to St. Marys Hospital late in July because of pulmonary embolism secondary to thrombophlebitis in the left leg. This responded to appropriate therapy. Neurologic examination at that time was normal except for his disorientation and the previously mentioned right temporal field defect.

If there are no further comments, this meeting is concluded with thanks to those who participated in the discussion.

Hugh D. Greer, III, M.D.*
Richard F. Galbraith, M.D.*
Juergen E. Thomas, M.D.*
George P. Sayre, M.D.*
Rochester, Minnesota

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Never tell evil of a man, if you do not know it for a certainty, and if you know it for a certainty, then ask yourself, "Why should I tell it?"—Lavater

Almost any system of government will work if the people will.

Every time a man engages in argument he loses a drop of blood from his liver.
—Persian proverb

Gray hair is a sign of age, not of wisdom.—Greek proverb

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Advances

Bacteremia:
Microbes, Manifestations, and Methods of Management

Part I - Coccal Infections

WILLIAM J. MARTIN, M.D.*
Rochester, Minnesota

UNDER CERTAIN circumstances almost any bacterial species can produce bacteremia. However, our present concern is with the organisms more frequently responsible, as well as with some less commonly encountered microbes, which have received special attention in the literature as being causative of bacteremia. Infections in which antibacterial therapy is unavailing are not considered herein.

Knowledge of the location of a primary nidus of infection, of the existence of an underlying, predisposing disease, and of any prior therapy may suggest the type of pathogen likely to be responsible for a given case of bacteremia. Such information may allow initiation of more reasonable antibacterial therapy until definitive microbiologic data are forthcoming, and also may be important in determining other aspects of management, such as surgical drainage.

The principles of management of patients having bacteremia can be summarized as follows: (1) procurement of samples of blood for adequate microbiologic study, (2) initiation of treatment empirically if the condition of the patient warrants, (3) re-evaluation if in vitro bacterial susceptibility tests later indicate poor choice of an antimicrobial regimen, but continuation of the regimen unaltered if the patient is doing well, (4) in selected infections, determination of the possible additive value of combined antimicrobial therapy, (5) in severe infections, procurement of serum bactericidal tests in a further attempt to determine if the bacteria are eradicable by the antimicrobial regimen employed, (6) administration of the drug or drugs in adequate dosage for a sufficient time, and (7) correction of any condition predisposing to, or complicating, the infection.

The antibacterial regimen selected for use in a given instance depends on many factors, such as the severity of the infection, the patient's general condition and resistance, his allergic diathesis, and his ability to accept the regimen by the route designated. In general, combinations of antibacterial agents should be reserved for situations that demand treatment while microbiologic data are awaited, for polymicrobic infections, and for instances of bacteremia wherein there are indications that an enhanced effect is possible.

Staphylococcal Bacteremia

In a series of 109 patients with bacteremia, but without endocarditis, due to Staphylococcus aureus, it was found that less than 10 per cent had had no preceding operation or recognized underlying illness.[1]

Preceding Illness

Of the 51 nonsurgical patients in this group, 13 had carbuncles, furuncles, or cellulitis, nine had malignant lesions, seven

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*Section of Medicine, Mayo Clinic and Mayo Foundation.

had diseases of the genitourinary tract, five had "collagen diseases," and four had generalized cutaneous disease. Thirty-two of the 44 patients in whom invasion of the bloodstream occurred after operation had undergone surgical procedures on the genitourinary tract. Seven of the remaining surgical patients had undergone orthopedic or neurosurgical procedures, and five had had operations on the gastrointestinal tract. It was somewhat surprising that only two patients in this series had diabetes mellitus, since this disorder has been encountered in about 10 per cent of patients having bacteremia due to gram-negative bacilli.[2]

Conditions of a suppurative nature, such as epidural abscess, septic arthritis, and purulent pericarditis, occurred in 12 patients and were classified as metastatic complications of the bacteremia. Hypotension (bacteremic shock) was noted in four patients.

Antibiotic Treatment

It is well known that no antibiotic is a panacea for staphylococcal bacteremia. However, dextrous manipulation of the antibiotics to which these organisms remain sensitive allows a reasonable chance of obtaining satisfactory results. It is generally agreed that penicillin G remains the most effective agent in the treatment of staphylococcal bacteremia, provided the organisms are sensitive to it.

Definitive treatment of staphylococcal bacteremia should be based on the results of in vitro tests for bacterial susceptibility. In more than half of patients with no previous hospital contact, the infecting Staphylococcus is sensitive to the action of penicillin G.

The need for agents with the potential of methicillin and oxacillin is not so great in staphylococcal bacteremia as in staphylococcal endocarditis. It is generally accepted that eradication of staphylococcal endocarditis requires use of agents capable of bactericidal effect, but this requirement does not appear mandatory for eradication of staphylococcal bacteremia. The bacteriostatic agents erythromycin and novobiocin have been effective in staphylococcal bacteremia; since these agents have been about as effective as penicillin G had been prior to the emergence of penicillin-resistant strains, it will be welcome but surprising if methicillin and oxacillin prove more effective. There is no gross objection to the use of methicillin or oxacillin when cultures indicate a Staphylococcus to be causative of bacteremia, but before the results of susceptibility tests have been reported; when these results become available, one can re-evaluate the regimen accordingly.

If the Staphylococcus resists the action of penicillin G (requiring more than 1.0 mcg./ml. for inhibition) and is sensitive to erythromycin, this drug may be the agent of choice since it is virtually nontoxic. Next, one considers novobiocin. If neither erythromycin nor novobiocin can be used, then methicillin or oxacillin may be the drug of choice. When these drugs are not applicable, as in patients who have known allergy to penicillin, kanamycin may be tried. Kanamycin precedes consideration of vancomycin since, while both are ototoxic, kanamycin is given intramuscularly while vancomycin is given intravenously. Even though chloramphenicol can be absorbed when given orally, it follows vancomycin in choice because of its propensity to depress the bone marrow; however, it precedes consideration of ristocetin, which also has a hematotoxic effect but has the added disadvantage of requiring intravenous administration. Before or after consideration of chloramphenicol and ristocetin — the decision may depend on one's fear of ill effects on the marrow or it may depend on the laboratory facilities that are available — one can consider combined antibiotic therapy. If such therapy is chosen, one of the so-called bacteriostatic agents, such as erythromycin, novobiocin, or chloramphenicol, is used, together with a bactericidal agent, such as bacitracin, kanamycin, or neomycin. However, the need for such cumbersome therapy is less common with the present availability of several effective antistaphylococcal agents.

Because of the effect of the tetracyclines on the bodily flora, with possible superinfection due to resistant strains, we avoid giving these drugs to patients who have staphylococcal bacteremia. Streptomycin, to which staphylococci develop resistance rapidly, and polymyxin B and colistin, which lack significant anti-staphylococcal action, usually are not considered in the treatment of staphylococcal bacteremia. Of the chemotherapeutic agents, nitrofurantoin, whose concentration in the blood is minimal and fleeting, and sulfonamides, to which the organism tends to be resistant, play no major role in the management of this infection.

Indiscriminate use of methicillin and oxacillin must be avoided. Since the degree of resistance to an agent is correlated with the amount of the drug being used in a geographic region, and since resistance to these agents has been demonstrated in vitro, the incidence of resistant strains may increase. Also these agents should not be used in patients who have had allergic reactions to other penicillins, since cross-allergenicity is known, nor should they be used in patients with allergic diseases, particularly asthma, unless need is over-riding.

Newer Anti-Staphylococcal Agents

The semi-synthetic anti-staphylococcal penicillins appear to be but bellwethers of similar drugs. In this regard, nafcillin is absorbed on oral administration and while it produces lower concentrations in blood, it persists in the body longer than oxacillin.[3] Preliminary investigation indicates that exceptional amounts of nafcillin are excreted in the bile, and it has been theorized that its depot effect may reflect containment in the hepatobiliary system. Another semi-synthetic anti-staphylococcal penicillin under investigation is cloxacillin.[3] This new agent appears to be better absorbed than oxacillin on oral administration. Still another orally administered semi-synthetic penicillin displaying activity against staphylococci is diphenicillin,[3] preliminary investigation of which has given encouraging results. However, none of the newer semi-synthetic anti-staphylococcal penicillins available to date have given irrefutable evidence of being capable of displacing methicillin and oxacillin in the therapeutic armamentarium. Continued investigation of available and future compounds of this series will be necessary before definitive conclusions are possible.

Cephalothin,[3] a cephalosporin C derivative, which is administered intramuscularly, is active against many micro-organisms, including penicillin G-resistant staphylococci. Fusidic acid[3] is an orally administered antibiotic, the antibacterial spectrum of which also includes penicillinase-producing strains of Staph. aureus. Continued investigation of these two agents may result in their being included in the anti-staphylococcal armamentarium in the near future.

Streptococcal Bacteremia

In 34 cases of streptococcal bacteremia without endocarditis, encountered during a 15-year period, Streptococcus pyogenes was the offending organism in 15 cases, Str. mitis in eight, and Str. faecalis in 11.[4] In six of this last group, other organisms were found along with the Str. faecalis, including Staph. aureus in one case, Escherichia coli in two cases, and Proteus vulgaris in three.

Preceding Illness

In half of the patients with bacteremia due to Str. pyogenes there was evidence of preceding suppurative conditions elsewhere in the body, such as otitis media with mastoiditis, streptococcal pharyngitis, and erysipelas. Complications of streptococcal bacteremia were noted only in those patients whose infection was due to Str. pyogenes. In this regard, suppurative polyarthritis was noted in two cases (one patient also had suppurative ophthalmitis), mycotic aneurysm in one, and acute hemorrhagic nephritis in two.

Of the eight patients whose bacteremia was due to Str. mitis, two had undergone surgical procedures. One had had mastectomy and the other, transurethral resection. Two of the eight patients had diabetes. One infant had omphalitis and peritonitis. Another patient had pyelophlebitis and peritonitis. Three of these patients had had preceding sore throats.

Ten of the 11 patients whose bacteremia was due to Str. faecalis stand in sharp con-

Continued

trast to the remaining patients of the streptococcal series in that the apparent portals of entry were solely gastrointestinal or genitourinary. Of the six patients whose infection may have arisen via the genitourinary tract, five had undergone transurethral resection or manipulation and one had had a penetrating hydatid mole necessitating hysterectomy. Of the four patients in whom the gastrointestinal tract appeared to be the likely portal of entry, one each had had acute gastroenteritis, biliary stricture, gastric resection, and carcinoma of the colon. The remaining patient in this group had had teeth extracted.

Incidence

In 1938, in a review of cases of bacteremia seen at the Mayo Clinic in a three-year period, the bacteremia in 61 of 144 cases was found to be due to hemolytic streptococci. In the more recent review, only 34 patients were noted with bacteremia due to all types of streptococci.[4] Therefore, the incidence of streptococcal bacteremia encountered at this clinic apparently has decreased from more than 20 cases annually to slightly more than two since the advent of modern antibacterial era. The decreased incidence of streptococcal bacteremia may be related to the action of antibacterial agents in eliminating the infectious precipitants of that condition. Employment of these therapeutic agents in patients with such conditions as otitis media and streptococcal pharyngitis as well as their judicious administration for patients who have recently undergone surgical treatment and who have streptococcal infections appears to hinder the bacteria from invading the bloodstream.

Antibiotic Treatment

Twenty-one patients with subacute bacterial endocarditis due to Str. mitis were given antibiotic therapy at this clinic in a two-year period; this indicates an occurrence of about one case per month.[5] In a ten-year period, 33 patients with enterococcal endocarditis were treated, and this indicates an occurrence of about one case every four months.[6] It is obvious, then, that in the recent past streptococcal endocarditis has been encountered considerably more often at the Mayo Clinic than streptococcal bacteremia without endocarditis.

In treating bacteremia due to Str. pyogenes, 1,000,000 units of procaine penicillin G given intramuscularly every 12 hours produces satisfactory results. We are continuing to evaluate the possible enhanced effect of treatment with a combination of a penicillin compound and a streptomycin compound in bacteremia due to Str. mitis and Str. faecalis. In our studies on streptococcal endocarditis it appeared that a combination of penicillin and streptomycin often had increased bactericidal effects when compared with the effect of penicillin alone. In attempting to combat bacteremia due to Str. mitis, we have reported that 1 gm. of streptomycin and 1,000,000 units of procaine penicillin G given intramuscularly every 12 hours yield satisfactory results. However, because of the potential auditory toxicity of streptomycin, some members of our group, including the author, currently prefer to use lesser amounts of the drug or none at all; we administer correspondingly increased amounts of penicillin in the management of bacteremia due to Str. mitis.

In regard to the use of streptomycin in bacteremia due to Str. mitis, and in infections of the bloodstream due to certain other organisms to be discussed subsequently, the following generalizations are pertinent. There is less danger of toxic effects from the use of streptomycin in the amounts mentioned in the presence of normal renal function since treatment usually does not exceed two weeks. If renal function is less than normal, the dose of streptomycin should be reduced or eliminated. It is not known with certainty if prior use of streptomycin or of other potentially ototoxic drugs such as kanamycin, neomycin, and vancomycin increase the possibility of an untoward otic reaction on future exposure to streptomycin, but it appears wise to consider this possibility in prescribing the drug in certain cases. In patients who have suffered ototoxicity on prior use of streptomycin, one avoids further use of that agent if at all possible. It has become apparent that in some cases of bacteremia, such as certain infections due to

Str. mitis, use of streptomycin may not be mandatory or the drug can be used in lesser amounts. The general condition of the patient, results of serum bactericidal tests, the patient's response to a given regimen, and similar factors may influence the administration and dose of streptomycin. Thus, while auditory toxicity may follow use of streptomycin, the statistical incidence of such is minimized if one avoids a dose in excess of the patient's renal tolerance and administers it for a minimal period. Fear of toxicity should not be such as to interdict its use completely, but, at the same time, one should not employ it unnecessarily or indiscriminately.

Since most strains of Str. faecalis are more resistant to penicillin than are the other strains of streptococci, usually we use at least 10,000,000 units of penicillin G together with up to 2 gm. of streptomycin daily when attempting to eradicate that organism.

When a patient requires more than 6,000,000 units of penicillin daily, one usually resorts to continuous intravenous administration. In such cases, one divides the total daily dose of crystalline penicillin G into equal parts and dissolves each half in 1 liter of 5 per cent dextrose in distilled water. To each liter of solution there is added 25 mg. of heparin in an attempt to decrease the incidence of chemical phlebitis. The apparatus for administering the solution usually can be adjusted so that the two liters are given in 24 hours.

If doubt arises as to the merit of the regimen being used in a case of enterococcal bacteremia, the so-called serum bactericidal test may be used. In this test, the patient's serum containing the given antibiotics is assayed against the organism isolated from the patient's bloodstream. If the patient's serum, diluted one to four, does not produce a bactericidal effect on the organism, one increases the dose of penicillin in increments of 10,000,000 units until such an effect is produced.

As in most other types of bacteremia, in streptococcal bacteremia treatment is continued until three successive negative blood cultures have been obtained and the patient has remained afebrile for at least 72 hours.

If bacteremia due to Str. faecalis is associated with a gram-negative bacillus, it appears advisable to initiate antibiotic therapy empirically with one of the tetracycline group of compounds in addition to penicillin and streptomycin. If in vitro susceptibility tests later indicate that the choice of tetracyclines is not optimal, the program can be re-evaluated.

In patients allergic to penicillin, erythromycin or a tetracycline may be effective in streptococcal bacteremia. However, since a considerable number of hemolytic streptococci and enterococci resist the action of the tetracyclines, these cannot be used routinely in bacteremia due to such organisms.

The prognosis is relatively good for patients with streptococcal bacteremia without serious underlying disease if adequate amounts of penicillin alone, or penicillin in combination with streptomycin, are given.

Pneumococcal Bacteremia

Bacteremia due to Diplococcus pneumoniae may occur during the course of pneumococcal pneumonia, particularly when the infection is fulminating. Endocarditis, most commonly involving the aortic valve, may complicate pneumococcal pneumonia and is characterized by persistent pneumococcal bacteremia. In pneumococcal meningitis at least 50 per cent of patients have bacteremia due to D. pneumoniae. However, invasion of the bloodstream by pneumococci in the absence of pneumonia, endocarditis, or meningitis is unusual.[7] The incidence of pneumococcal bacteremia has greatly decreased since the advent of modern antibacterial therapy. Penicillin G is the drug of choice; the route of administration and daily amount, which may be several million units, are dependent in part on the presence or absence of associated endocarditis or meningitis. In patients allergic to penicillin, erythromycin may be given; again, an associated lesion may indicate substitution of a regimen with a bactericidal effect.

Neisserian Bacteremia

The clinical management of bacteremia

Continued

due to Neisseria meningitidis virtually is inseparable from that of meningococcal meningitis. A sulfonamide in full dosage or aqueous crystalline penicillin G in amounts of 1,000,000 units every four to six hours by intramuscular injection may be used. However, one should be aware that in vivo and in vitro resistance to sulfonamides has been described recently in strains of Neisseria meningitidis.[8] The question of penicillin-resistant strains has been raised from time to time, but thus far the problem appears not to have any great clinical significance. If the incidence of sulfonamide-resistant or penicillin-resistant strains increases, perhaps penicillin and a sulfonamide should be given conjointly, at least until in vitro susceptibility data are available in the case at hand. If meningitis is suspected, larger amounts of penicillin should be given. The possibility of supervening vascular collapse should be borne in mind constantly.

Neisseria gonorrhoeae rarely succeeds in invading the bloodstream. Large doses of penicillin are recommended if invasion occurs.

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Physical Differences

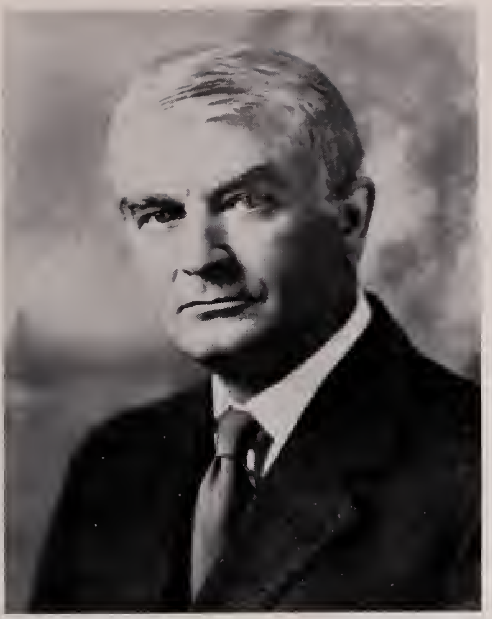
Amongst the chief essentials — indeed the elementary basis, as it were, of the whole subject of hygiene is the fact that there are among people a great many different constitutions; and this is acknowledged by all doctors and gymnasts. For my part, I prove this by actual results; people who have before been constantly ill I keep free from disease by persuading them to follow hygienic precepts. Thus, some I forbid to take any exercise at all — that is to say, exercise by occupations — as I consider the ordinary functions of life enough for them. Some I order to abstain from excess of exercises, so as to reduce the whole to the smallest limits; some only to change the kind of exercises, or the order, or the time; some to alter their entire plan. Similarly, I give advice about bathing — either not to bathe at all, or more than before, or less, and only before meals, or also after meals; or with colder or warmer water than usual. Thus I have kept people well for a great number of years.

Yet I would have done none of these things if I had not known their natural physical differences, and the hygienic regimen appropriate to each.

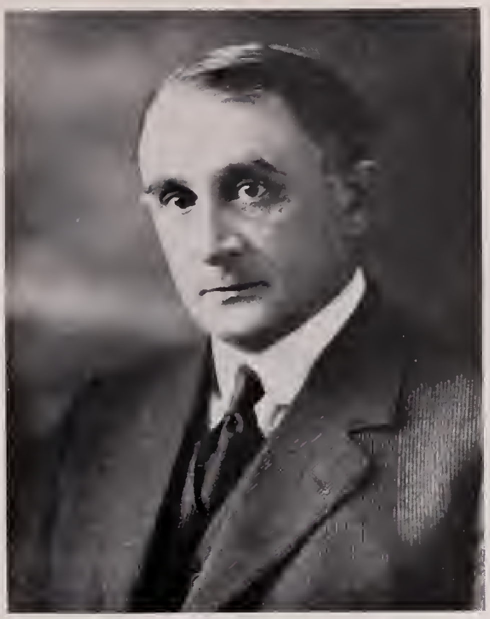
— Claudius Galen. 200 A.D.

Circumstances are the rulers of the weak; they are but the instruments of the wise.

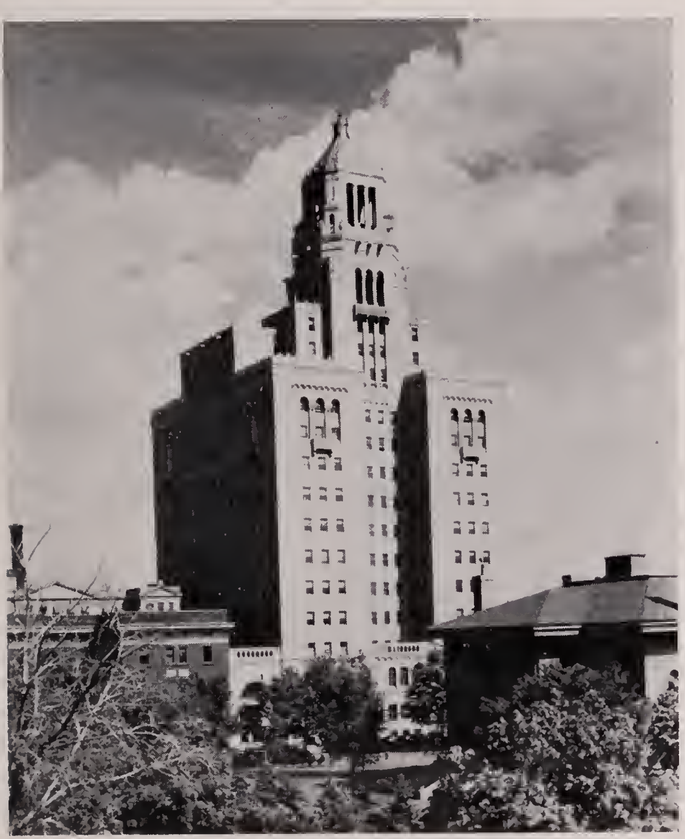
—Samuel Lover



William James Mayo, M.D.
1861-1939



Charles Horace Mayo, M.D.
1865-1939



Plummer Building, Mayo Clinic

The Brothers Mayo

A Photographic Essay

Clark W. Nelson, Archivist
Mayo Clinic

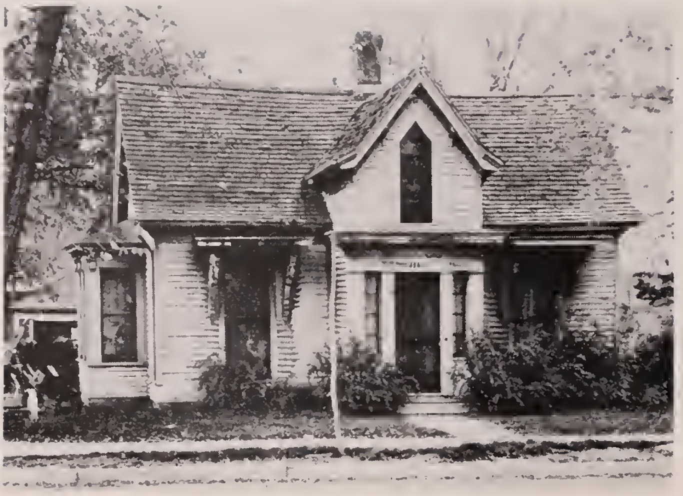


Figure 4

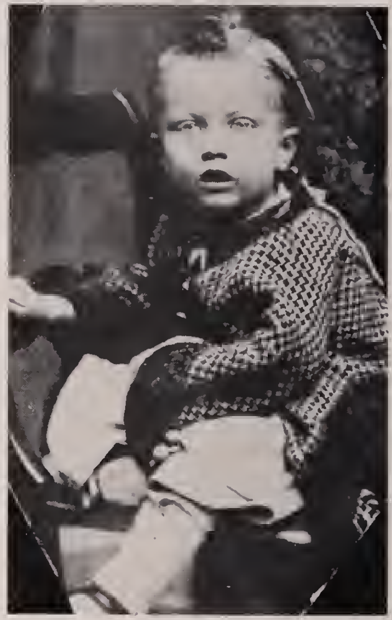


Figure 5

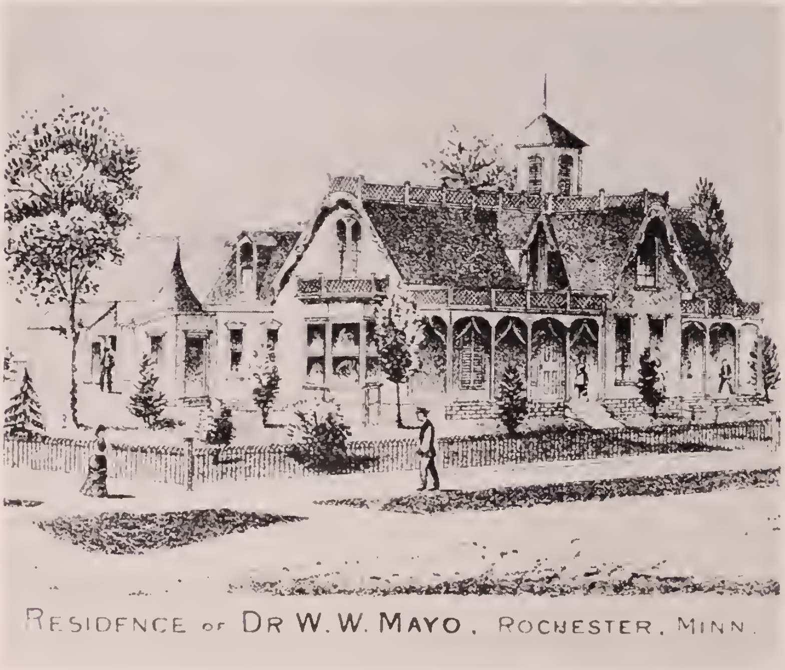
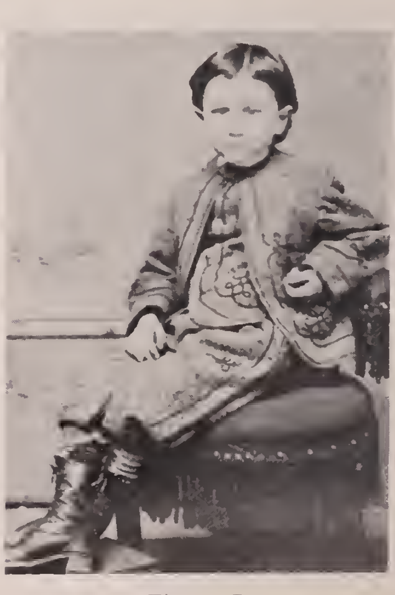

RESIDENCE OF DR W. W. MAYO, ROCHESTER, MINN.

Figure 6

Will Mayo (5) was born on June 29, 1861, in this house (4) in LeSueur, Minnesota. Four years later, the family moved to Rochester where Charlie (7) was born in this home (6) on July 19, 1865.



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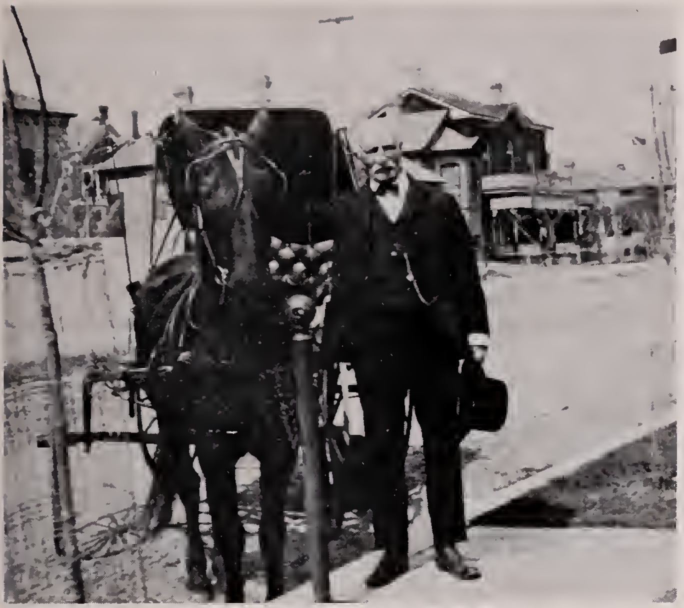


Figure 8

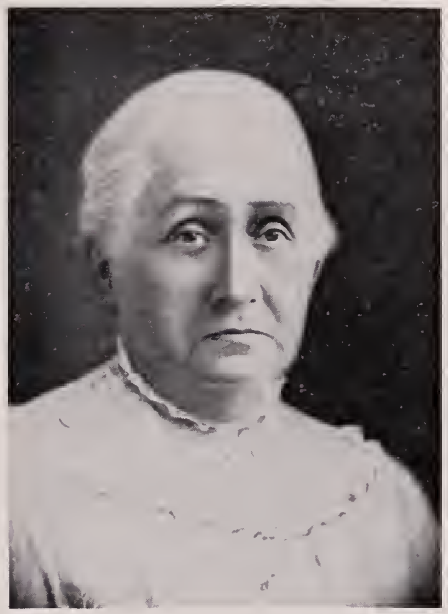


Figure 9

The brothers grew up in the frontier town of Rochester (10). Here they were a part of Dr. (8) and Mrs. (9) William Worrall Mayo's family. Here they learned their first lessons in medicine from father.

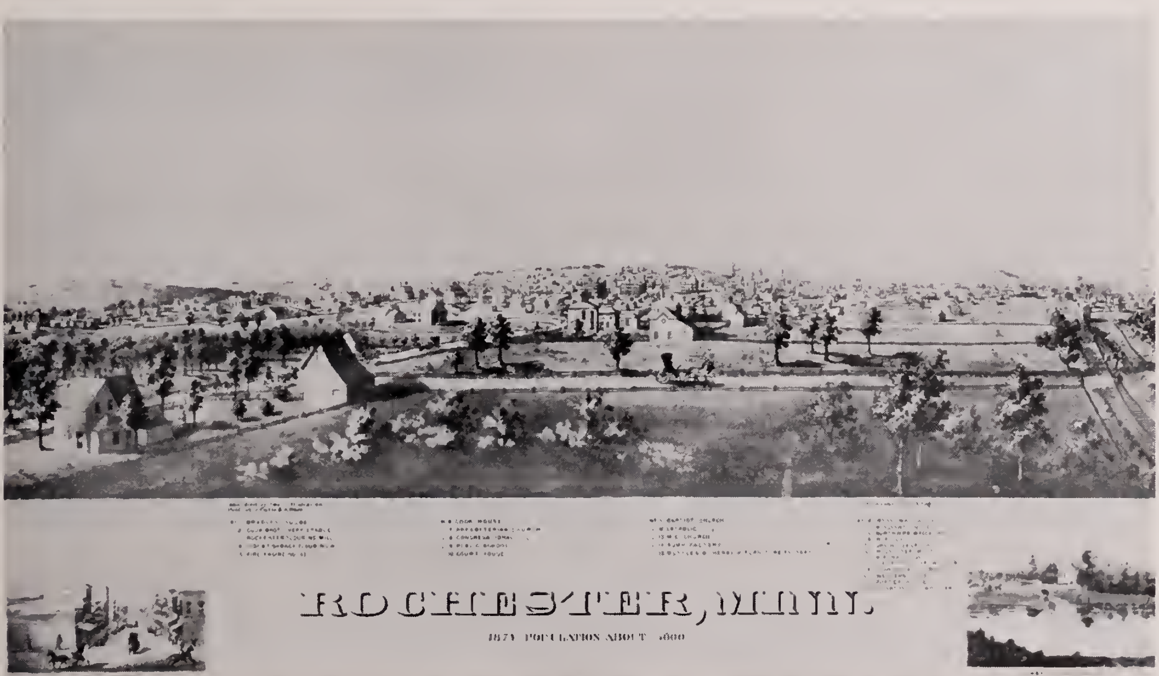
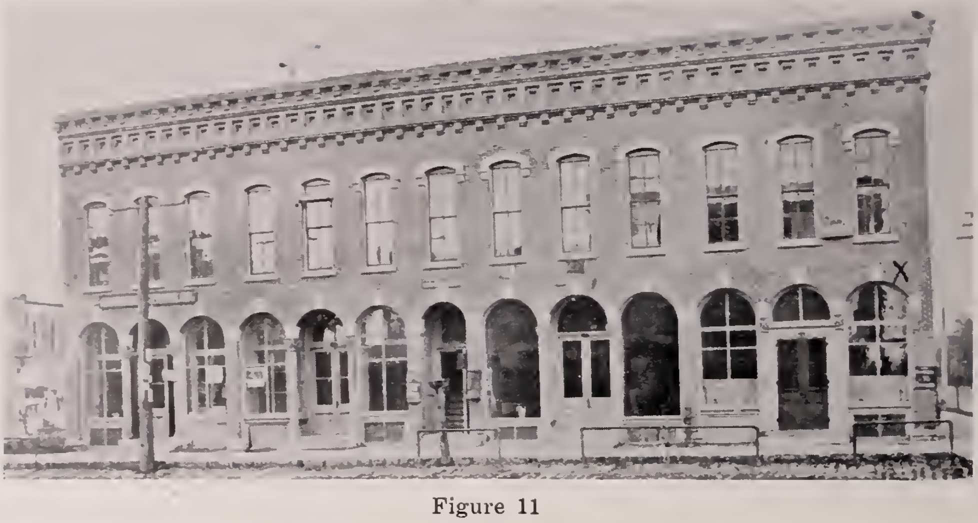

ROCHESTER, MINN.
POPULATION ABOUT

Figure 10



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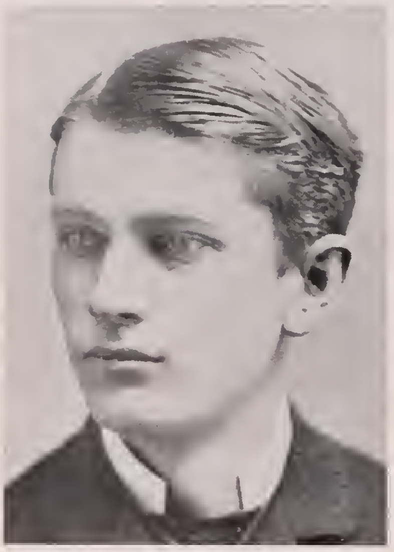
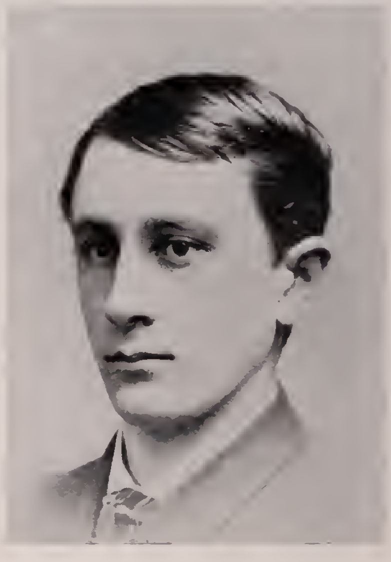


Figure 12

From 1881-1883 Will (12) attended medical school at University of Michigan and from 1885-1888 Charlie (13) studied at Chicago Medical College, an affiliate of Northwestern University. The two young doctors then returned home to practice with their father (14). At this location, they began the family practice that eventually became the private group practice of the Mayo Clinic (11).



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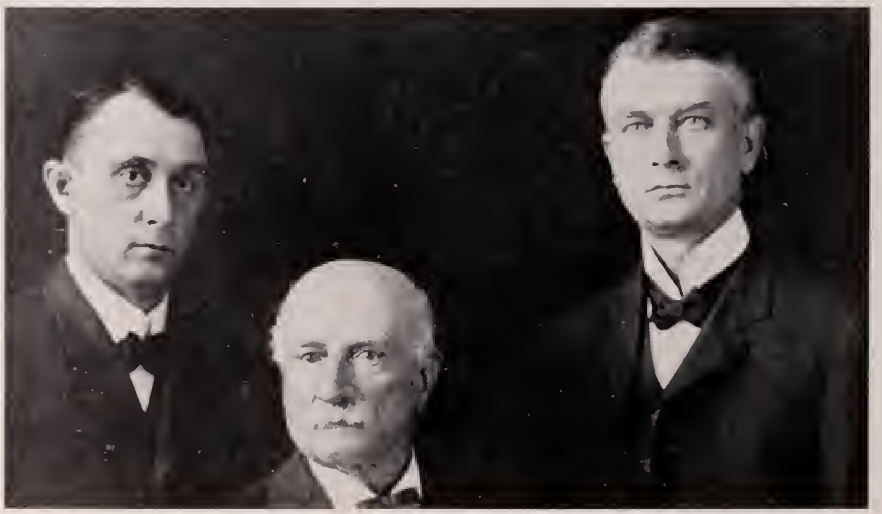

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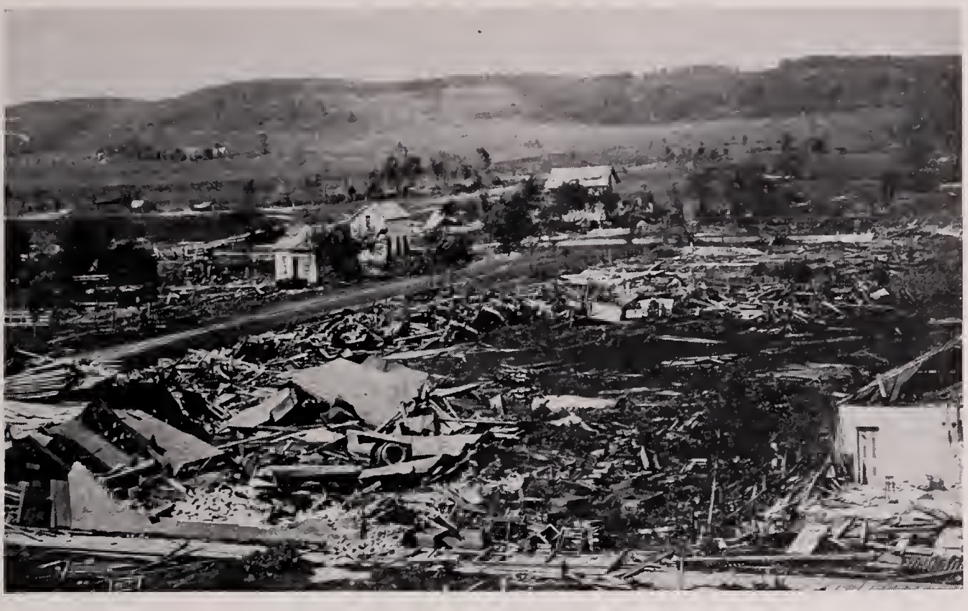

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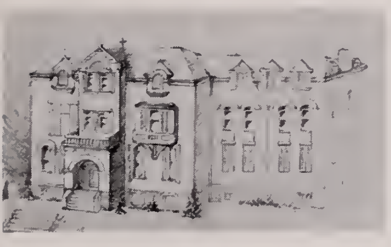
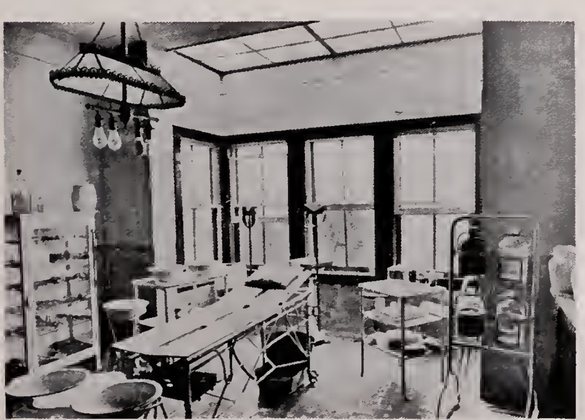


Figure 16

In 1883 a tornado (15) focused attention on the need for a hospital in Rochester. In 1889 the Sisters of St. Francis completed the first building (16) of St. Marys Hospital. Here in its operating rooms (17), the brothers (18) attracted worldwide attention with their surgical skills.



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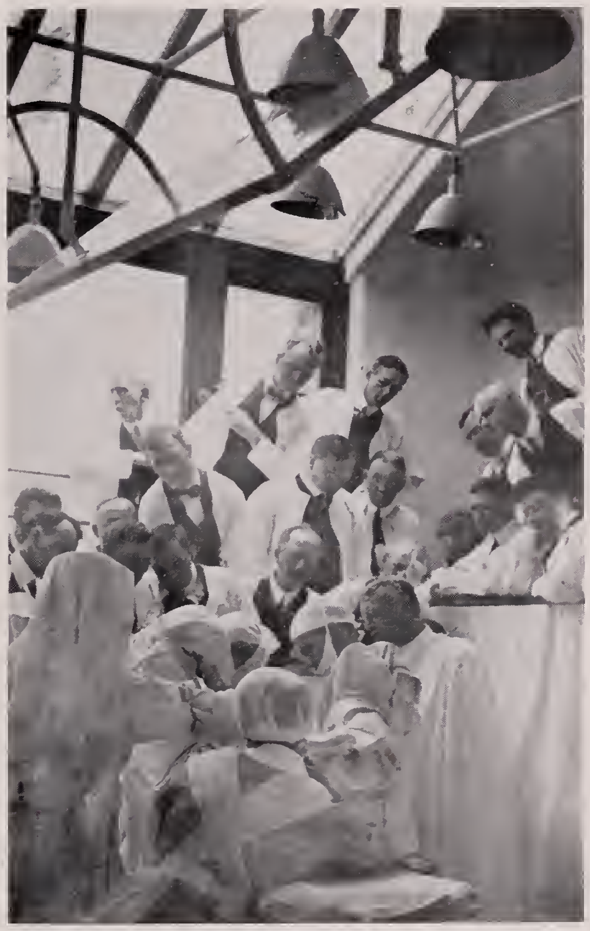

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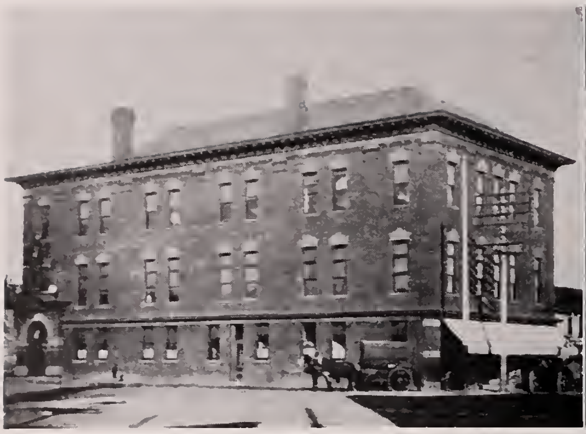

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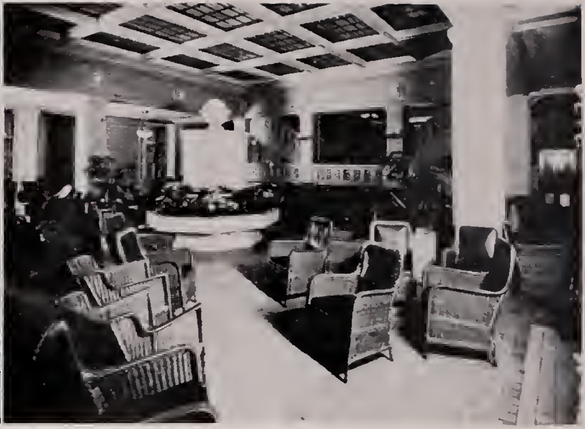
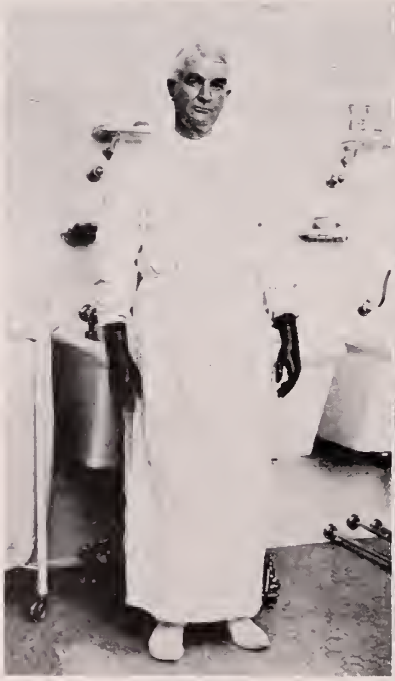


Figure 20

From offices in the Masonic Temple Building (19), the brothers (21) (23) expanded into a specially constructed office building in 1914 (20). This first Mayo Clinic structure was followed by a larger one in 1928 (22). These two buildings brought together surgical, medical, and laboratory consultants as a team.



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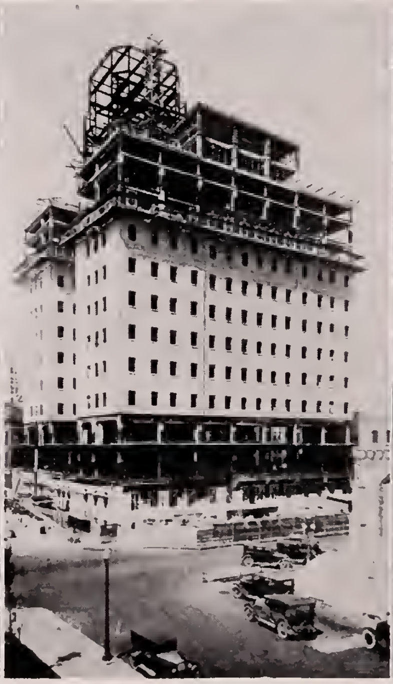

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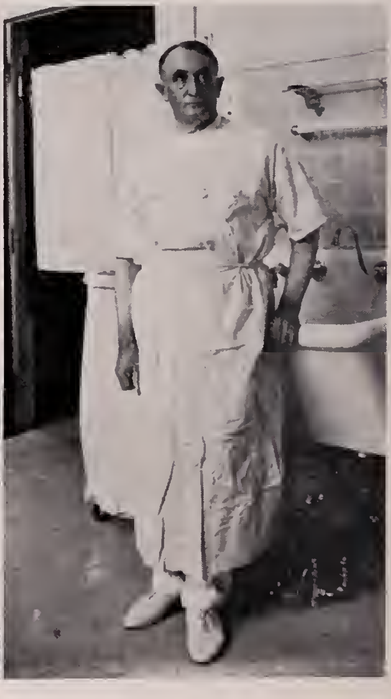

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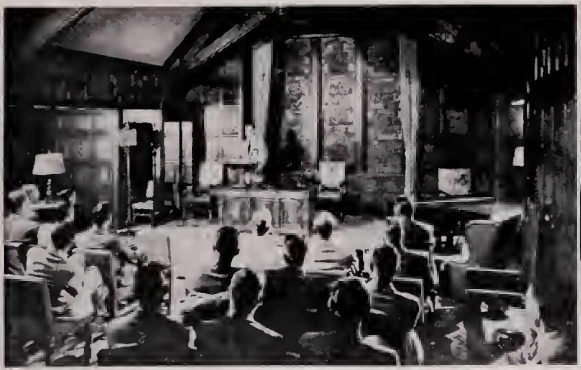

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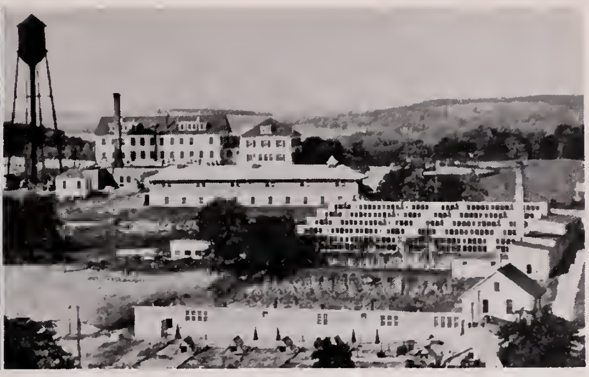


Figure 25

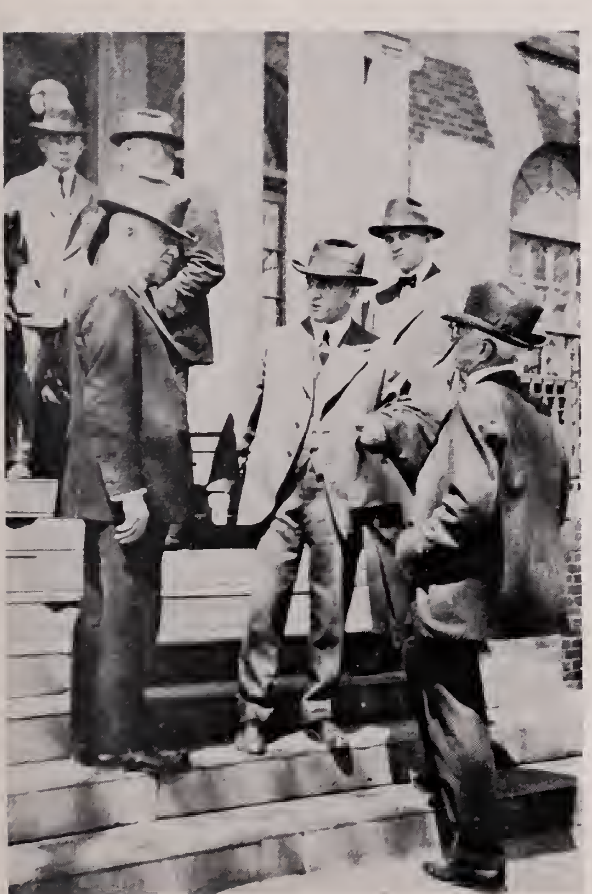


Figure 26

Realizing the need for research and education in medicine, the Brothers Mayo (26) established the Mayo Foundation for Medical Education and Research. Fellowship programs (24) were undertaken for graduate medical training and an Institute (25) of Experimental Medicine constructed to aid in research.

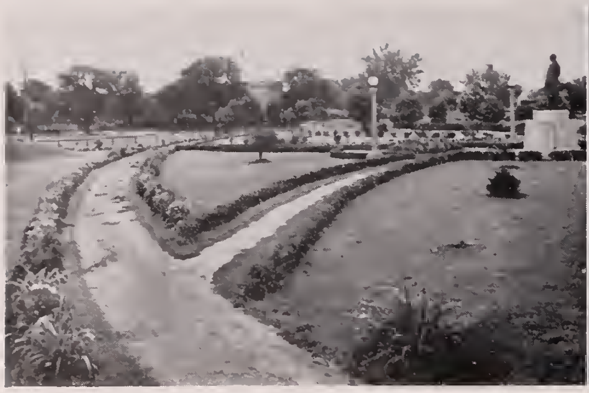


Figure 27

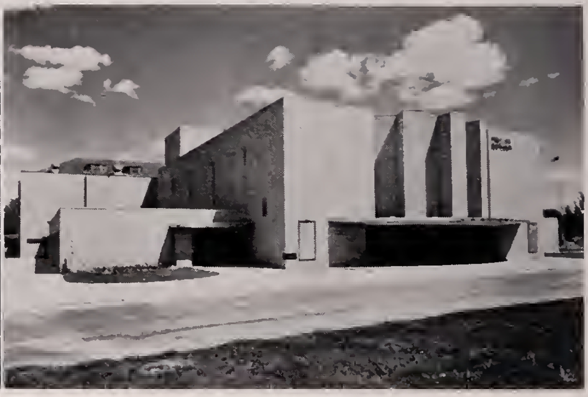


Figure 28

Both brothers were active in supporting the development of their community, state, and nation. To Rochester they gave land for parks, (27), an auditorium (28), and an airport (29).

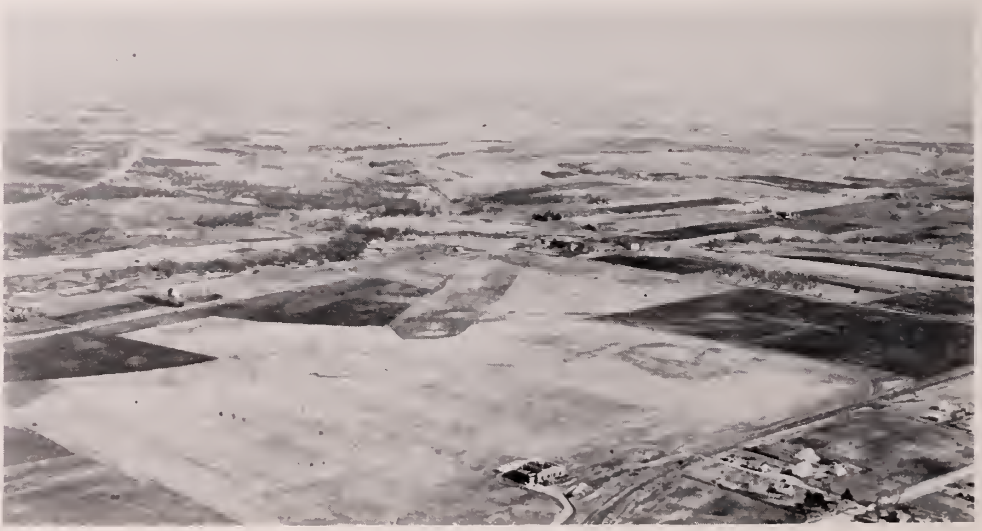


Figure 29

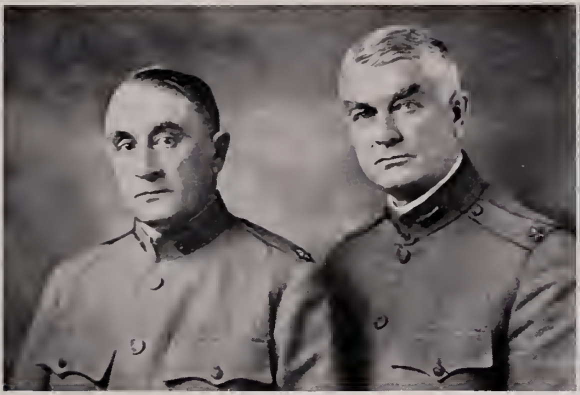


Figure 30

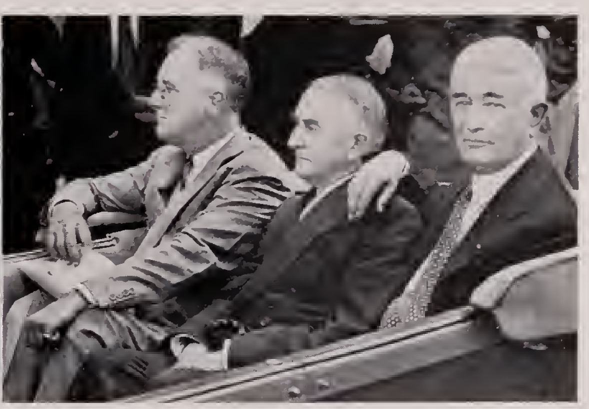


Figure 31

During their lives, many honors were received. They were made Brigadier Generals in the armed services (30). In 1934 the President of the United States came to Rochester to honor them (31). On this occasion President Roosevelt presented a bronze plaque for distinguished service from the American Legion (32).

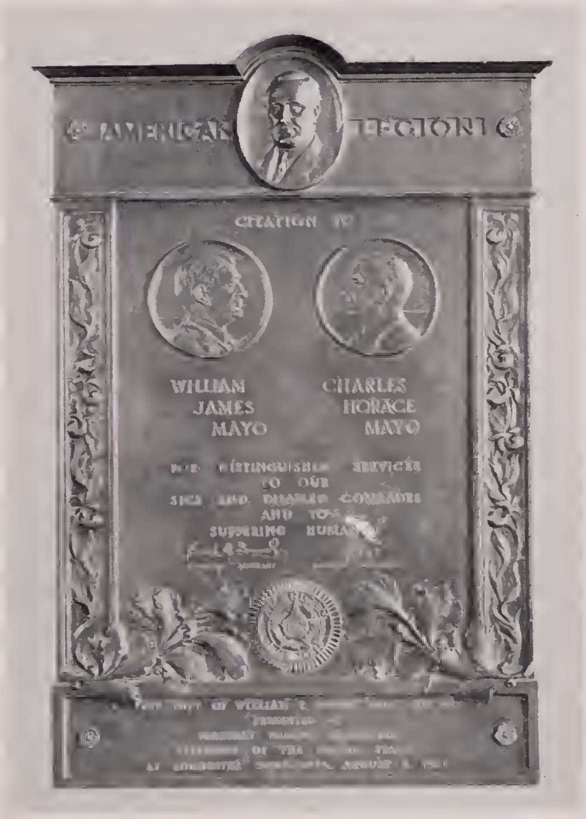
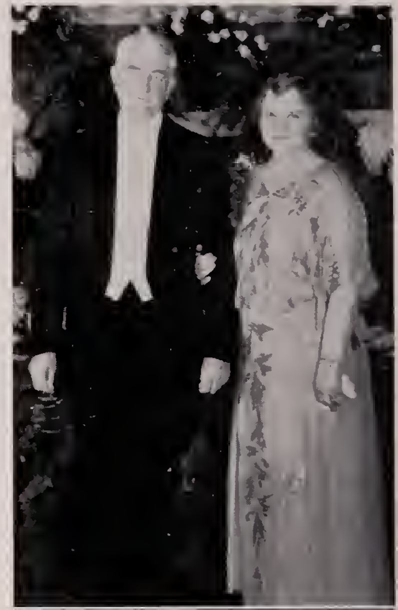
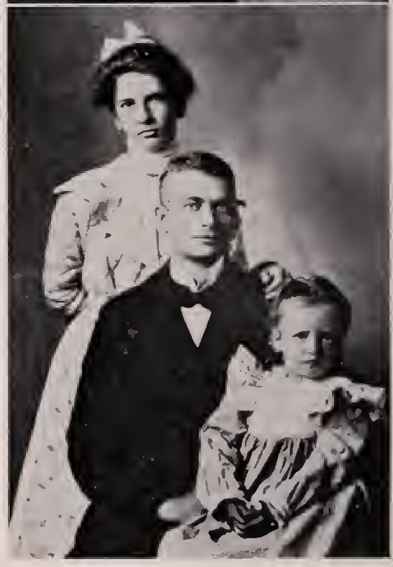

AMERICAN LEGION
CITATION TO
WILLIAM JAMES MAYO
CHARLES HORACE MAYO
FOR DISTINGUISHED SERVICES
TO OUR
SICK AND DISABLED COMRADES
AND TO
SUFFERING HUMANITY

Figure 32

Figures 33 (top) and 34 (bottom)

Both doctors were devoted family men. Dr. Charlie married Rochester's first trained nurse, Edith Graham Mayo (33). Their family (34) was raised at Mayowood (37), designed by Dr. Charlie himself. Dr. Will spent over 50 years of married life with Hattie Damon Mayo (35). Together with their daughters (36), they lived in a house (38) that they later gave to the Mayo Foundation.





Figures 35 (top) and 36 (bottom)

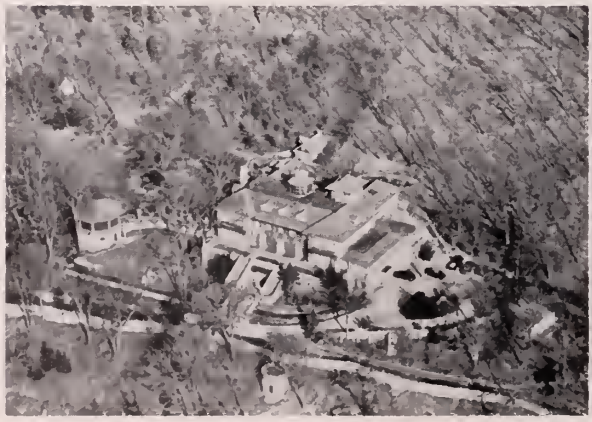


Figure 37

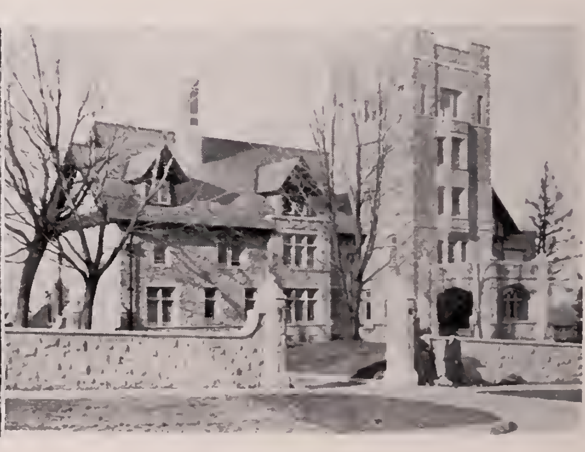


Figure 38

Grand Rounds

Diabetic Retinopathy

Treatment by Hypophysectomy

Rapidly progressing retinopathy is one of the major complications of diabetes.[1] The pathophysiology of diabetic retinopathy is related to alterations in lipids, glycoproteins and hormonal balance, and is not yet clearly understood. Recent studies by Blumenthal[2] suggest that the various components of diabetic glomerulosclerotic lesions contain an anti-insulin complex and that this vascular complication may be related to an immune phenomenon with insulin as an antigen. Coleman[3] demonstrated that fluorescent insulin may be bound specifically to the retinal capillary aneurysm, the basement membrane of the ciliary body and iris in eyes with diabetic retinopathy.

Methods of Treatment

Houssay discovered in 1931 that extirpation of the adenohypophysis partially alleviated experimental diabetes in animals and clearly demonstrated that this gland has great influence on the regulation of carbohydrate metabolism. The possibility that acquired or induced decrease in pituitary function would beneficially influence the progression of diabetic retinopathy was raised by Poulsen's report in 1953 of a woman who improved in her retinopathy after the development of Sheehan's syndrome.[4] Several procedures have been used to induce pituitary ablation: hypophysectomy, stalk section, and Y^{90} implantation.

Hypophysectomy

According to Luft,[5] the transfrontotemporal approach should be used

Continued

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*Presented as a Medical Grand Rounds at Mt. Sinai Hospital, Minneapolis, November, 1963.

only by surgeons with great experience with hypophysectomy in nondiabetic patients; otherwise, extracranial procedures are preferred, and of these, transantrosphenoidal hypophysectomy or implantation of Y^{90} have proved best. Fraser[6] has recently reported on yttrium implants for diabetic retinopathy (11 cases). The irradiation must deliver over 100,000 rads to the pituitary. With the slightest errors in placement, the diaphragm may be necrosed and cerebrospinal fluid may escape into the sella and out through the needle hole so that rhinorrhea may develop. Inserting screws in the old puncture sites as a second operation may correct the rhinorrhea.

Section of the Stalk

Stalk section has been used by Field[4] and Fager[7] via the transfrontal route. Following low section of the pituitary stalk, the hypophyseal end is dissected free of the opening in the diaphragm and then curetted out of the fossa, taking with it a small portion of the pituitary gland at the attachment of the stalk itself. The hypothalamic end is left undisturbed and the opening in the diaphragm coagulated. Field places a gold foil over the sella so as to prevent re-establishment of hypothalamo-hypophyseal portal circulation and serve as a shield for the optic chiasm, should addition of a radiation source become desirable.

Irradiation

Linfoot et al.[8] have used pituitary irradiation with alpha particles in the treatment of Cushing's disease. These heavy particles provide a more satisfactory form of teletherapy than X rays or gamma rays. Larger amounts of ionizing radiation and a greater biologic effect can be delivered safely to the sella, with little scatter and a favorable skin depth dose relation. This is also an alternative technique for the treatment of diabetic retinopathy. According to Sprague,[9] studies provide little encouragement for further use of adrenalectomy as a means of palliating diabetic retinopathy or other diabetic vascular disease.

Selection of Cases

Criteria for hypophyseal stalk section according to Field[4] were as follows: If a patient was a possible candidate after initial screening examinations, serial observations at one to two-month intervals were made until an extrapolation of the rate of advance of retinopathy indicated that loss of useful vision would ensue within a predictable period of one to six months. At this point the patient was admitted to a research and metabolic ward and assessment of all pertinent functions was made. The following criteria were used:

Progressive Retinopathy

Documented progressive retinopathy, advancing fast enough to threaten loss of useful vision within a relatively short predictable period of time.

Macular Changes Reversible

Patients with advanced neovascularization, fibrotic changes and active hemorrhagic tendency were acceptable, provided at least one macular area was present in which complete deterioration had not occurred or in which the character of the macular changes was still reversible.

Postponement Factors

Rejection or postponement of consideration if any of the following were observed: bilateral complete irreversible macular destruction or deterioration from any cause, massive vitreous bleeding in which no satisfactory views of the macular areas could be obtained, retinopathy in which hemorrhagic phenomena were not a major factor, retinopathy with a very slow tempo of advance or which was shown to be stable.

Rejection Factors

Any of the following findings served to eliminate the patient as a candidate:

1. Creatinine clearance consistently below 60L/24 hours, fixed azotemia, and albumin below 2.5 gm. A predominant element of pyelonephritis on renal biopsy, more than moderately advanced arteriolar disease or hyalinization of glomeruli, and refractory urinary tract infection.
2. Fixed cardiomegaly, extensive or active myocardial disease, overt or borderline cardiac failure, fixed arrhythmia, or angina pectoris.
3. Chronic incurable infection anywhere.
4. Incapacitating peripheral or visceral neuropathy.
5. Personality, character or emotional instability or intellectual deficit of a degree that indicated inability to adhere to a demanding regime of medication, diet and periodic examination. An important, almost intangible criterion is the intensity of the patient motivation toward the procedure. Unless there was clear understanding of what was involved and an affirmative choice without persuasion was obtained, the patient was ruled out as a candidate.

Results

Favorable changes in the eyes of the patients treated by Field[4] consist of:

1. *Clearing of vitreous haze which may be objectively apparent within 48 hours after operation.*
2. *Cessation of vitreous hemorrhagic activity.*
3. *Loosening and reabsorption of previous fixed collection of blood in preretinal spaces or vitreous.*
4. *Condensation and attenuation with increased translucency of proliferative glial tissue.*
5. *Decreased caliber of previously engorged veins.*
6. *Apparent self-occlusion and disappearance of fronds and retes of fine neovessels.*
7. *Disappearance of rubeosis iridis.*
8. *Migration of exudates outwards from the macular region.*

The net result has been objective improvement of visual acuity.

Sprague has recently made a review[9] of eleven reports of American, English, Swedish, and Danish investigators: "A total of 134 cases were reported. The procedures employed were hypophysectomy (103 patients), hypophyseal stalk section (20 patients) and yttrium implantation (11 patients). In some cases, particularly in the earlier treated cases, it was so advanced as to leave little possibility of improvement of vision even if the process were arrested by induction of pituitary insufficiency.

Continued

Mortality

Among the total 134 cases, there were 15 postoperative deaths or 11.2%. With the improved criteria for selection of patients and increasing experience in medical care average mortality can be expected to decline.

Improvement in Vision

Among the 119 patients who survived, there was a favorable effect in 75 individuals. In some of these there was a measurable improvement in vision, while in others there was arrest or apparent slowing of the progression of retinopathy. According to Sprague the over-all benefits of the procedure in the entire group were lessened by subsequent death of 39 patients at intervals up to six years following the induction of pituitary insufficiency. Thus at the time of the reports 80 of the original 134 patients were alive. The most frequent causes of late deaths were renal disease (20 patients), hypoglycemia (11 patients), and coronary or other vascular disease (6 patients).

Incomplete Removal

Incomplete removal or destruction of the pituitary diminishes favorable results. The experience of Javid et al.[10] casts some doubt on the effect of stalk section because of the results in two cases. In one patient necrosis was very extensive and in the other a very small area of necrosis was found at autopsy. "Perhaps because of variation in the vascular supply, namely anastomosis between the superior and inferior hypophyseal arteries, this variability may account for the observation that section of the pituitary stalk is not parallel to hypophysectomy functionally as far as improvement in vision and alteration in endocrine assays."

Postoperative Complications

Postoperative complications include cerebral abscess, facial nerve paresis, transitory oculomotor paresis, staphylococcal meningitis, orthostatic hypotension and carotid artery damage with transitory hemiparesis.[11,12]

Hypophysectomy does not affect diabetic neuropathy.[13,14] Calcifiication of peripheral vessels is not affected by hypophysectomy.[5] Insulin requirements are frequently reduced.[5,9,15] Severe hypoglycemia has been a complication.[16] The endocrine changes after hypophysectomy for diabetic retinopathy have been studied by several investigators.[1,4,12] Amenorrhea developed in almost all women, thyroid function frequently decreased so that hypothyroidism developed, and the excretion of ketosteroids diminished. Diabetes insipidus in Anshie's series[1] occurred in all patients beginning between the second and 22nd postoperative day; when it appeared early diabetic control and fluid management were complicated. It was possible to discontinue pitressin after one to eight months. Most patients showed little ketonuria. Replacement therapy has been 6 mgm. of Prednisone, thyroxin 0.3 mgm. daily, testosterone in males, and estrogen in females.

Comments

"The mechanism by which interruption of pituitary function may arrest the course of retinopathy remains unknown. The mechanism seems to be related to the amelioration of the diabetes in terms of insulin requirements.

Stabilization of adrenal cortical function has been suggested as a mechanism but the evidence is not convincing. It has been speculated that removal of the source of growth hormone may be responsible, but experimental support is still lacking."[9] Perhaps hypophysectomy affects the immune mechanism related to the etiology of diabetic retinopathy. The natural course of diabetic retinopathy is so variable that no suitable controls can be provided for evaluating hypophysectomy adequately.

Hypophysectomy for diabetic retinopathy is still in an experimental and investigative stage, and for the present probably should be done only in selected patients at large centers, where the procedure is under study.[17-19] Adrenalectomy as a treatment has received only little interest.[20]

Case Report

This 32-year-old white male was admitted to Mount Sinai Hospital on September 18, 1963, and discharged October 12, 1963. Diabetes was discovered during February 1962 when he consulted his physician because of weakness of the right upper extremity following an injury at work. At that time he had a mild polydipsia, polyuria, and polyphagia. He was referred for an eye evaluation on March 16, 1962. Examination at that time indicated vision to be 20/50 in the right and 20/200 in the left eye. Proliferative diabetic retinopathy was present. On careful diabetic control encouraging improvement occurred. The newly formed blood vessels were seen in many areas to disappear and the patient's vision was maintained. The right eye appeared improved but the left eye had begun to show proliferating change in the vitreous. On March 21, 1963, vision in the right eye was 20/25 and the left eye had only light perception.

The patient returned on September 17, 1963, indicating that early that day he had noticed streaks in his right eye vision. At this time vision in the right eye was still 20/30. Fundus examination of the right eye indicated a very large retinal hemorrhage, which had not yet broken through into the vitreous. The left eye showed no significant change.

He was admitted to the hospital on September 18, 1963, and was placed on a 2,000 calorie diabetic diet and 20 units of Lente insulin daily.

Admission laboratory results were: Hb 16.2gm.%, leukocytes 5,300 with a normal differential. Urinalysis: sp. gravity 1.025, pH 5, no albumin or glucose. VDRL negative. EKG was normal. Chest X ray was normal. Co_2 30 meq/L, Cl meq/L, 103 meq/L, Na 140 meq/L, K 4.3 meq/L, 17-ketosteroids 19.6 mg.$_2$24 hours, FBS 122 mg.%, BUN 21 mg.%, albumin 4.4 gm.%, globulin 3.7 gm.% cholesterol 221 mg.% BSP 4%, PBI 5.7 mcg%, PSP 26% at 30 min., 24-hour urine for protein negative.

Prior to surgery blood glucose determinations were near normal.

On September 27, 1963, a right transfrontal craniotomy and sectioning of the pituitary stalk was performed. A thin tantalum sheeting was placed over the diaphragm sellae. Immediate postoperative course was excellent. On September 28, 1963, the patient had a temperature of 102 which slowly subsided. On October 4, 1963, he developed a fever of 101. Urinalysis showed 10 to 15 WBC's and 50 to 75 RBC's, and a culture revealed pseudomonas. He was placed on Mandelamine and the fever gradually subsided.

On September 28, 1963, the patient had begun to put out large amounts of urine, up to 8,150 cc., with a sp. gravity of 1.001 to 1.005. The diabetes insipidus was controlled with pitressin tannate in oil, 0.5 ml. every 24 hours. He was maintained on prednisone 2.5 mgm t.i.d., Lente insulin 20 units daily, and thyroid 3 grains daily.

Vision in the right eye after surgery was 20/20. The left eye vision was only light perception. Three weeks after surgery the patient developed a hemorrhage in the right eye which broke through the macula. No change in the left eye had occurred at that time.

Aaron Kerlow, M.D.
Mt. Sinai Hospital

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1. Anshie, D., et al.: Surgical Hypophysectomy for Diabetic Retinopathy. Diabetes 11:463, 1962
2. Blumenthal, H. T., et al.: The Pathogenesis of Diabetic Glomerulosclerosis. I. and II. Diabetes 11:296, 1962.
3. Coleman, J. L., et al.: Fluorescent Insulin Staining of the Diabetic Eye. Diabetes 11:375, 1962.
4. Field, R. A., et al.: The Effect of Hypophyseal Stalk Section on Advancing Diabetic Retinopathy. Diabetes 11:465, 1962.

5-20 can be obtained from the author.

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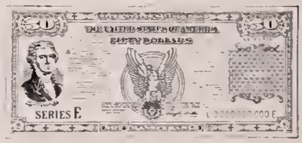

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Industrial Medicine

The Attitude of the Medical Witness

For those who engage in industrial medicine and are required to testify in court from time to time, there are a few simple, common-sense rules which it would be well to keep in mind.

The medicolegal symposium of the American Medical Association devised the following set of Do's and Dont's:

1. *Do* take the role of the medical witness seriously. The courtroom is a place in which practical men are engaged in the serious work of endeavoring to administer justice. The role of the medical witness is a key one in this endeavor.

2. *Don't* agree to or accept compensation for your services contingent upon the outcome of litigation. This practice is unethical and its disclosure would be apt to destroy the value of your testimony.

3. *Do* insist on preparation for your testimony in consultation with the attorney for the party who called you as a witness. He should advise you on what to expect on cross-examination. You have a right to consult with the party and his attorney about the case, so, don't be embarrassed if asked about such consultation.

4. *Don't* act as an advocate or partisan in the trial of the case. If the attorney for the party who calls you as a witness needs the advice or guidance of a doctor during the trial, let him employ another doctor. Disclosure of partisanship of a witness strongly tends to discredit his testimony.

5. *Do* be as thorough as is reasonably necessary under the circumstances in examining a party in preparation for trial. Exhaustion of all possible tests and procedures may not be required, but be prepared to justify any omissions.

6. *Don't* exaggerate. Any attempt to puff up your qualifications or to elaborate the extent of the examination you have made is apt to be exposed, to your embarrassment.

7. *Do* inform the attorney for the party who called you as a witness of all unfavorable information developed by your examination of the party, as well as the favorable information.

8. *Don't* try to bluff. If you don't know the answer to a question, don't guess. If you guess wrong, you may be falling into a trap.

9. *Do* be frank about financial arrangements with the party who called you as a witness, with respect to your compensation for both treatment given and services in connection with the litigation.

10. *Don't* regard it as an admission of ignorance to indicate that your opinion is not absolutely conclusive or that you don't know the answer to a particular question. Honesty may frequently require testimony of this nature.

11. *Do* answer all questions honestly and frankly. Any display of embarrassment or reluctance to answer will tend to discredit your testimony.

12. *Don't* use technical terminology which will not be understood by the jury, the attorneys, or the judge. If technical terms are unavoidable, explain them the best you can in the language of the layman.

13. *Do* be willing to disagree with so-called authorities if you are convinced that they are wrong. If you have sound reasons for disagreement, the contrary opinion of authorities will not necessarily discredit you.

14. *Don't* be smug. A jury is quite likely to react adversely to an attitude of this nature. A modest attitude on the part of a witness is apt to elicit a more favorable response.

Continued

Leave it to the attorney to bring out your special qualifications.

15. *Do* be courteous no matter what the provocation. If a cross-examining attorney is discourteous to you, this is apt to win sympathy for you from the jury, provided that you don't descend to the same level.

16. *Don't* lose your temper. If a cross-examining attorney can provoke you to a display of anger or sarcasm, he has already substantially succeeded in discrediting your testimony.

17. *Do* pause briefly before answering a question asked on cross-examination, to give the other attorney an opportunity to object to the question if he so desires. Taking a moment for deliberation before answering a question does not indicate uncertainty or embarrassment.

18. *Don't* allow yourself to be forced into a flat "Yes" or "No" answer if a qualified answer is required. You have a right to explain or qualify your answer if that is necessary for a truthful answer.

President's Letter Continued from Page 1039

unusually fine. They show great promise of even further improvement. Dr. J. Arnold Bargen, Chairman of the Council on Postgraduate Programs, is playing a large part in promoting the excellence of the programs in both the science and the art of medicine for the betterment of public health, and the medical care of the American people. He is doing much of this by stimulating the various sections of the Association to increase their efforts in regard to the annual program by and through the leadership of the section secretaries.

Dr. Bargen was President of your Association in 1957, when he was Chief of a Medical Section at the Mayo Clinic. Former Governor Freeman was a guest at the annual dinner that year and Admiral Rickover was the principal speaker. Because Dr. Bargen was busy and I had a slight acquaintance with both men, he asked me to introduce them to each other. I did this with only moderately comminuted fractures of protocol but was well rewarded for my unskilled effort. Instead of the usual acknowledgment of an introduction, the Admiral made inquiry as to the Governor's age. As I recall the incident, the Governor replied that he was then 37. Whereupon he was given an excellent lecture on the responsibilities of young men in high offices, with emphasis on the aspect of politics versus service. An enjoyable discussion for me to hear as both of them talked well.

The foregoing reminds me that Dr. Stickney, your President-Elect, is already hard at work on the program for the State meeting in 1965, with the help of the Committee on Scientific Assembly. They are also discussing long-range ideas for the general up-grading of our annual meetings. The general format can be altered only slowly, if they decide changes are indicated, because of the commitments for space and time which must be made years in advance.

Perhaps by next month, some issue for discussion may arise.

J. P. Medelman M.D.

J. P. Medelman, M.D.
President
Minnesota State Medical Association

Epilepsy

The treatment of epilepsy has advanced more in the past 25 years than in the previous 2500. Yet many people still regard epilepsy cases as "hopeless," according to The Epilepsy Foundation. For facts on this little-understood malady write to: The Epilepsy Foundation, Washington, D. C., 20005.

Abstracts, Briefs and Commentaries

MALIGNANT PAROTID TUMORS

A series of 74 cases of parotid gland carcinomas from the experience of Toronto General Hospital, over the period 1932 to 1956, has been reviewed. The major pathological groupings were adenocarcinomas, mucoepidermoid carcinomas, and malignant mixed tumors.

The incidence of malignancy in parotid tumors at this institution was about 20%, inasmuch as there were 213 patients during this period who had benign parotid tumors.

The net five-year survival rate was 53%. The authors stress, however, that parotid malignancy may manifest chronicity and that patients may harbor and die of the disease beyond the five-year period. Also discussed is the occasional difficulty in deciding on pathological grounds whether a mixed tumor is benign or malignant.

Survival rates appear to be better in younger people and in women. Rapid growth, large size, occurrence of pain, facial palsy, and node metastases are all ominous findings. Since the majority of cases of parotid tumors do not present with these adverse findings, the authors stress the need for early diagnosis by pathological examination of the symptomless, mobile, parotid mass.

Mucoepidermoid malignancies have the most favorable outlook while the adenocarcinomas have the poorest prognosis.

Preoperative biopsy is condemned because of the danger of transplanting cancer cells. The treatment of choice is considered to be conservative parotidectomy followed by irradiation. In their experience radical excision with sacrifice of the facial nerve, even when supplemented by irradiation, has not saved any of the ten patients to whom it was applied. Neck dissection is suggested only where involved nodes are apparent.

Robert N. Hammerstrom, M.D.
Minneapolis, Minn.

Mustard, R. A. and Anderson, W.: Malignant Tumors of the Parotid. Ann Surg 159: 291, 1964.

REPORTING OF RESULTS OF RABIES IN BATS

In a recent communication from the Communicable Disease Center, U. S. Public Health Service, the following statement appeared in connection with a case of bat rabies:

> "Since rabies virus is known to occur in salivary glands in (these) animals without being present in their central nervous system, it is imperative that all bona fide bat bites receive post exposure vaccine treatment unless the salivary glands, as well as the brain tissues, are specifically examined and found to be negative."[1]

The laboratory of the Minnesota Department of Health has been aware of the above-stated hazard and subsequent to August 1962 bat salivary glands, as well as brain tissue, have been examined for rabies virus. Fluorescent antibody smears are made of these tissues and the salivary glands and central nervous system tissue are both used in mouse inoculation tests to detect the presence of virus.

During the year 1963 a total of 34 bats were submitted for diagnosis of rabies. The results of these examinations are shown in the table below. The brain of number (2) was not examined because the bat's skull had been fractured and brain tissue was not recognizable. No salivary glands were examined from (3), as the skull was crushed and the salivary glands could not be identified.

Results of Laboratory Examination of Bats for the Presence of Rabies Virus,
Minnesota Department of Health
1963

	Result		
Tissue Examined and Method	Negative	Positive	Total
(1) Brain and Salivary Gland, FA and Mouse Inoculation	(a) 29	(b) 1	30
(2) Salivary Glands Only Examined, FA and Mouse Inoculation	1	0	1
(3) Brain Only Examined, Mouse Inoculation	1	0	1
Total	31	1	32
(4) Unsatisfactory for Examination 2			

In the past, bat specimens in class (a), (2) and (3) would be reported to the physicians as negative for rabies. In view of the Communicable Disease Center statement, it is apparent that there would be a slight risk of developing rabies for the patient exposed to a bat (as with number (3)) whose salivary glands were not examined for rabies virus, if he did not receive post-exposure vaccine treatment. Consequently a new policy of reporting has been established.

In the future when the laboratory is unable to examine the bat's salivary glands for the presence of virus, and the brain is negative, the report card sent to the physician will read as follows:

Negative — unable to examine salivary glands which could contain virus. If bona fide bat bite, post-exposure vaccine treatment should be advised.

Bats are the only animals that have been shown to excrete virus in the salivary glands when no virus can be demonstrated in the brain tissue. To protect persons bitten by bats from unnecessary post-exposure vaccine treatments the Division of Medical Laboratories, Minnesota Department of Health, is examining salivary glands as well as brain tissue for virus whenever possible. In cases where the salivary glands can not be examined, the physician will be so notified in order to recommend post-exposure vaccine treatment to fully protect his patient.

R. N. Barr, M.D.
Dept. of Health

1. Morbidity and Mortality, Weekly Report, U. S. Department of Health, Education, and Welfare, Public Health Service, Communicable Disease Center, 12, November 1, 1963, p. 364.

SURGICAL TREATMENT OF ACUTE TRAUMATIC RUPTURE OF THE THORACIC AORTA

The authors report on the successful early surgical correction of three patients with traumatic transection of the aorta just at the isthmus level. Two of the three cases survived. The diagnosis of aortic transection was suspected on standard chest X ray which indicated widening of the superior mediastinum. This was confirmed by aortography in each of the cases.

The possibility of rupture of the thoracic aorta should be considered in all victims of severe vehicular accidents, in crushing chest injuries with a hemothorax and a murmur over the left upper chest. Oftentimes delayed symptoms of chest pain, further widening of the mediastinum, hoarseness, or dysphagia suggest that secondary aortic bleeding has occurred. Aortography can be accomplished safely, effectively, and conveniently by transeptal injection of the contrast medium to the left atrium.

The surgical technique included partial circulatory bypass from the left atrium to the femoral artery, which thus provided flow to the lower portions of the body and the spinal cord during the cross clamping of the aorta; however, the use of extracorporeal circulatory bypass had the distinct disadvantage of requiring anticoagulation in patients who had multiple other injuries. The authors suggested that an alternative protective procedure might be the combination of hyperboric oxygenation with hypothermia to avoid this problem.

Comment: The article again calls attention to a traumatic lesion of increasing incidence. With the greater number of vehicles on the road and subsequent deceleration of Juggernaut type of injuries, the outlying hospitals and physicians should become more suspicious of such injuries with patients who arrive at the hospitals in shock. Often the patient may have symptoms suggestive of central nervous system when actually these are pseudo-symptoms of central nervous system injury related to the secondary changes in the cardiovascular system subsequent to traumatic aortic injuries. Therefore, routine chest X rays, even if in the prone position or decubitus position, should be done in all such patients, as the outward evidence of thoracic injury is often very meager and overshadowed by the more extensive deformities of the extremity injuries.

Jerome T. Grismer, M.D.
Minneapolis, Minnesota

Fleischaker, R. J., Mazur, J. H., and Baisch, B. F.: J Thorac Cardiov Surg 47: 289, 1964.

HIGH OUTPUT RESPIRATORY FAILURE

Peritonitis is not a primary cause of death since it is possible to establish several more basic pathological abnormalities. Included among these is inadequate function of one or more specific organ systems such as the heart, the kidneys and the lungs. The authors focus their interest upon a type of respiratory failure that may occur with initially normal lungs.

Following a severe peritoneal insult, a balance is established between (1) The demands made on the patient's respiratory system and (2) The patient's ability to adapt to these demands. First, the inflammatory reaction leads to an increased tissue utilization of oxygen and thus an increased demand on the cardiorespiratory system and muscular work. Since these latter demands involve a significant rise in oxygen utilization, there is established a vicious cycle requiring more and more oxygen transport and CO_2 elimination. Secondly, the patient's total respiratory ability to respond to increased demands is decreased by high diaphragms, pain on respiration, early atelectasis in the lower lobes and fatique. Satisfactory compensation is therefore possible only if the decrease in respiratory reserve does not lower the patient's total respiratory ability below the level required by the increased energy demands. A patient may be able to compensate during the first few days following peritoneal insult only to succumb to respiratory failure at four or five days because the relationships of reserve and energy demand shift as time passes.

The authors have termed this early syndrome HIGH OUTPUT respiratory failure, indicating that it is characterized by inability to provide adequate tissue oxygenation despite an initially increased gas exchange. They have treated 21 patients with this type of failure. Initial attempts to establish adequate respiratory function were made by relief of intra-abdominal tension, oxygen therapy and tracheal suction. This approach was ineffective in 20 of 21 patients. Effective therapy was instituted with a tracheostomy and controlled ventilation with a mechanical respirator.

The authors believe that this is a particularly dangerous and often unrecognized syndrome that merits close attention.

Comment: This is a significant study. The authors distinguish this early form of respiratory failure from the later stage of pulmonary failure that is secondary to aspiration, pneumonitis or embolization. The distinction is important, since the former may be treated successfully with early relief of the intolerable work load of respiration.

D. S. P. Weatherhead
Minneapolis, Minnesota

Burke, J. F., Pontoppidan, H., and Welch, C. E.: High Output Respiratory Failure. Ann Surg 158:581, 1963.

THE SOLITARY PULMONARY NODULE

This is a summary of a co-operative study begun in 1959 among 78 hospitals of the Veterans Administration and the United States Armed Forces.

The definition of the "solitary" pulmonary nodule was (1) no definite preoperative diagnosis, (2) no symptoms referrable to the nodule, (3) nodule of any size under 6 cm., (4) calcium or cavitation could be present, and (5) other pulmonary disease unrelated to the nodule could be present.

There were nodules in 887 males that were studied and 882 nodules were resected. Preoperative studies were usually unrewarding. The only preoperative study which eliminated the possibility of a malignant neoplasm was *dense* or concentric calcification.

Fifty-six per cent of the nodules in men over fifty years of age were malignant. Of 882 nodules, 316 were malignant.

Delay of exploratory thoracotomy is not warranted in the patient with an isolated noncalcified pulmonary nodule. The smallest can be a malignant neoplasm.

J. T. Grismer, M.D.
Minneapolis, Minn.

Steele, J. D.; J Thor Cardiov Surg 46:21, 1963.

DUODENAL DIVERTICULUM

The records of a million patients at the Henry Ford Hospital in Detroit were reviewed and 1,064 patients with duodenal diverticulum discovered. This percent incidence roughly corresponds to other series reported in the literature, but is somewhat lower than the incidence found in autopsy material.

Only six of the 1,064 patients came to surgery. In four of them the removal of the duodenal diverticulum was an incidental procedure associated with other upper abdominal surgery. In one case the lesion was involved with diverticulitis and caused common bile duct obstruction. The sixth case had experienced repeated duodenal hemorrhage. The duodenal diverticulum showed no pathological changes, however.

The author emphasizes the hazards associated with duodenal surgery and suggests that primary surgery for duodenal diverticula be restricted to cases fulfilling one of the following criteria: Proven life-endangering hemorrhage, perforation, abscess formation, significant and persistent diverticulitis.

The author's conclusions regarding surgery for duodenal diverticula represent application of sound principles. When one is tempted to consider surgical removal of a duodenal diverticulum, which is not certain to be the source of a threat to life, he should carefully evaluate the probable higher incidence of complications resulting from the treated as compared to the untreated lesion.

Minneapolis, Minn.
Robert N. Hammerstrom, M.D.

Whitcomb, J. G.: Duodenal Diverticulum. Arch Surg 88:275, 1964.

ASPIRIN AND GASTROINTESTINAL BLOOD LOSS

The red blood cells of 15 normal human subjects were labeled with Fe^{59} and Cr^{51}, and the blood loss in the gastrointestinal tract was determined by counting each isotope in a homogenized aliquot of feces. Blood loss in each subject was measured during three randomized collection periods of eight days each: (1) control, (2) tablets of acetylsalicylic acid (aspirin), 2.5 gm/day, and (3) the equivalent amount of aspirin taken as a buffered solution of sodium acetylsalicylate. It is concluded that aspirin can cause gastrointestinal bleeding, which can be prevented by its administration as buffered solution.

Courtesy of References and Reviews
Journal of the American Medical Association

Leonards, J: Gastroenterology 44:617, 1963.

ETIOLOGY OF SARCOIDOSIS

From tuberculous patients and patients with sarcoidosis, bacteriophages lytic for tubercle bacilli were isolated. Whereas tuberculous patients were found to raise phageneutralizing antibodies, those with sarcoidosis appeared unable to do so. In vitro experiments showed that when neutralizing antibodies are absent, phagolysis and lysogenic conversion of tubercle bacilli proceed. Lysogenic conversion results in the emergence of bacilli so modified in their morphological and antigenic properties that, on the basis of the classical bacteriological criteria, they can no longer be recognized as tubercle bacilli. From six lymph node biopsies collected from patients with sarcoidosis and cultured on a variety of media, including media containing antiphage sera, five variant strains of tubercle bacilli were isolated. These observations support the view that certain cases of sarcoidosis are due to "modified" tubercle bacilli.

Courtesy of References and Reviews
Journal of the American Medical Association

Mankiewicz, E.: Canad Med Ass J 88:593, 1963.

BILIARY FISTULA

"A spontaneous internal biliary fistula connects the extra hepatic biliary tract with another abdominal viscus, usually the stomach, duodenum, or colon. It is called spontaneous because it is unrelated to surgery or trauma."

Autopsy findings indicate an incidence of 0.1% to 0.5%. At biliary operations fistula are found more often in 1.2% to 5% of cases. The variance is theorized to be due to the fact that many tracts heal spontaneously and that, unless the dissection is done carefully and a search made for a fistula, it will be missed. One surgical analysis of 819 cases found 51% to be cholecystoduodenal, 21% cholecystocolic, 19% choledochoduodenal. Cholecysto-gastric, choledocho-gastric and cholecysto-choledochal fistulae are more rare. "An internal biliary fistula does not develop in the absence of cholecystitis, gallstones, neoplasm or peptic ulcer." About 90% of these fistulae are associated with gallstones. Penetrating duodenal ulcer accounts for 6% and is often the cause of choledocho-duodenal fistula. Gallstones produce obstruction of the cystic or common bile ducts, causing recurrent attacks of cholecystitis. A fistula occurs when necrosis causes a rupture into an attached organ. It is rare that rupture involves two organs, though a cholecysto-duodeno-colic fistula may result. Patients are usually middle-aged or elderly females with a long gall-bladder history, or middle-aged men with a long history of chronic duodenal ulcer.

Symptoms

Symptoms include acute or chronic upper abdominal pain, obstructive jaundice, pyrexia, diarrhea if the fistula involves the colon, and vomiting if ileus is present. Some patients have hematomesis and melena if the erosion involves the gastric or duodenal wall. Stones which passed into the stomach have been vomited or passed with the stool. Obstructive jaundice may be improved when the fistula develops, but relief from pain may not occur. Local right upper abdominal rigidity and tenderness are usual.

Complications

Reflex cholangitis is likely to occur, and if the fistula involves the colon, permanent liver damage may result. Gall-stone ileus, or actual complete obstruction of the small bowel, may follow passage of a stone through the fistula. This complete obstruction may take place at any level; but if the stone travels far enough it may lodge at the ileocecal valve. If an obstructing stone remains in place long enough, perforation of the bowel results. Obstruction of the pylorus may result during the passage of a large stone from the stomach.

X ray may visualize the gas-filled gallbladder and ducts. The main hepatic duct and common duct may show as bubbles of gas. In that case the fistula may connect any part of the extra biliary drainage system to the duodenum, stomach or colon. Gas is less likely to pass to the biliary tract when the fistula joins the intestine. The hepatic and common ducts may be dilated by obstructive pressure.

The author describes X-ray methods of diagnosis by the use of gas from an ingested effervescent powder, and by the use of the opaque meal and enema, together with intravenous injections producing excretion, and visualization of the bile tract. Regurgitation of barium through an incompetent sphincter of Oddi can happen The cystic duct, the common duct and ampulla have been found sufficiently dilated to permit the passage of the index finger. These studies, besides determining if the primary cause for the fistula is in the biliary tract, also indicate the primary causes when there is visible a chronic ulcer of the stomach or the presence of a malignancy involving contacting viscera.

Many fistulae heal spontaneously when stones are passed and the patency of ducts and digestive tract persists. If the fistulae and ducts become obstructed, severe pain may develop, accompanied by jaundice and greatly increased hazard. Connection between the gallbladder and duodenum with patent channels is adequately treated by cholecystectomy and suture of the opening in the bowel. It is imperative that no stones are left in the common duct after any operation. Any fistulous tract involving the colon may be more infected and require preliminary preparation of the colon. Whichever surgical method is employed, the bile ducts and digestive tract must be patent when the operation is completed. Ulcer at the pylorus causing massive adhesions, stricture of the common duct and pylorus may demand exploration and drainage of the common duct with T tube drainage together with gastric resection and a Bilroth anastamosis.

A Facetted Stone

Intestinal obstruction by a facetted stone again means a search for more stones, the condition of patient permitting.

In discussion the author states that incompetent and dilated lower common duct and ampulla may give rise to air in the biliary tract. He quotes Cournoisier, who reported the passage of a gallstone four inches in diameter through the ampulla.

Stanley R. Maxeiner, M.D.
Minneapolis, Minnesota

Pitman, R. Y., Davies, Alan: The Clinical and Radiological Features of Spontaneous Internal Biliary Fistula. Brit J Surg 50:414, 1963.

Some doctors have much in common with God: They cannot be reached — even at the golf club.—Rabbi Heschel

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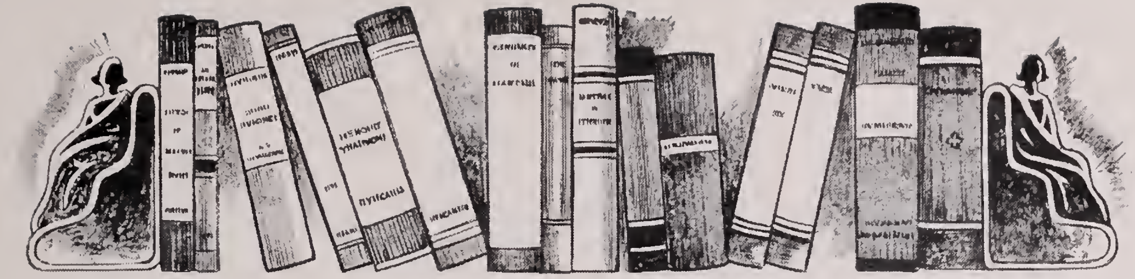

Book Reviews

Books are embalmed minds.—Bovee

CURRENT DIAGNOSIS AND TREATMENT — **Brainerd, Henry; Margen, Sheldon; Chatton, Milton J., Lange Medical Publications, Los Altos, California, 1964.**

This is the third edition of this publication, which, by its very nature of being a review book itself, rather defies summarization. However, the general format, several strong points, and the practical purpose of the book can be illustrated.

Included in each of the twenty-eight chapters, each of which is mainly constructed around an organ system, are a series of diseases and conditions related to that organ system. Each of these subdivisions consists of a "thumbnail sketch" of the disease or condition, its main presenting symptoms and signs, the necessary criteria to establish the diagnosis, a brief differential diagnosis, possible complication, and then the treatment, which of necessity becomes somewhat empiric.

The contents include tables of normal laboratory values, short discussions of drugs which are in use but are not as yet established, and a dissertation on heart-lung resuscitation in a step-by-step fashion. Among the strong points of this book is the chapter on fluid and electrolyte, which explains the basic physiologic principles of acid-base balance in an attempt to form a background for practical fluid therapy. In addition the chapters on dermatology, metazoan infection, and poisoning are constructed so as to simplify differential diagnostic problems in these areas.

The purpose of this book is not to function as a textbook, but as a handbook. It is constructed with a very complete table of contents and index, which lends itself to rapid reference. Then, the reference, once found, is intended to awaken the memory of the reader and alert him to possible diagnoses and complications.

The book is certainly of value to the physician who is just entering practice and lacks a certain amount of personal experience. It would be of value to anyone in the general practice of medicine, particularly in illuminating the seldom encountered problem, and by keeping him informed of new types of therapy.

Jean R. Eckerly, M.D.
Minneapolis, Minnesota

REVIEW OF MEDICAL PHYSIOLOGY — **William F. Ganong, M.D., Lange Medical Publications, Los Altos, Calif. 577 pages, price $6.50.**

Never before has so much useful information been offered for so little money. This is the much awaited addition to the Lange Review Series which has been so eagerly received by medical students and physicians. The complete gamut of human physiology is run with many references to clinical problems. The current work in this rapidly expanding field has been incorporated and referenced. Familiar illustrations from classical texts and articles have been reproduced along with many from the "Review of Physiological Chemistry" (9th Ed. 1963, Lange). The author is to be congratulated for this enormous effort. Care to know the atomic weight of Gadolinium, what happens when trained worms are fed to untrained worms? Want a two-page review of biostatistics or a concise breakdown on thyroid hormones? Make checks payable to the publisher. This is an invaluable reference work for all physicians as well as a complete study text for medical students. There is no comparable book available.

William S. McClanahan, M.D.
Minneapolis, Minnesota

SURGICAL CLINICOPATHOLOGICAL CONFERENCES OF THE MASSACHUSETTS GENERAL HOSPITAL — **Benjamin Castleman, M.D., John F. Burke, M.D., Little, Brown and Company. $12.50.**

This book of 50 surgical CPC's is worthwhile acquiring by the surgeon and the generalist. Since most surgical problems can be neatly fitted into the proper category one is apt, on occasion, to let his diagnostic acumen become less sharp than it should be. The value of these CPC's is to challenge the reader to upgrade the manner in which he approaches his day to day problems as demonstrated by the prominent discussers participating in each case.

X rays, photographs, photomicrographs, and illustrations are beautifully reproduced to add to the completeness of the presentations.

Harrison H. Farley, M.D.
Minneapolis, Minnesota

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Maternal Studies

Obstetric Infection Deaths in Minnesota*

Part II**

ALEX BARNO, M.D.***
Minneapolis, Minnesota

Septic Abortion

Of the 16 septic abortion deaths (Table 7), 10 or 63% were self-induced or criminal abortions. Five of these were illegitimately pregnant individuals and five were married. It is interesting to note the method by which these abortions were accomplished — catheter three, nut pick one, syringe one, glass tube one, plastic tube one, tapwater douche under high pressure one, and unknown two. All of these 10 had intrauterine and/or blood cultures (Table 7). Four showed gram-negative rods, three clostridium perfringens, one beta hemolytic streptococci, one E. Coli and beta hemolytic streptococci; and one was sterile (taken five days after antibiotic therapy). These 10 are tabulated as to the picture of septic shock, jaundice and anuria. Six of them were primary problems in the management of septic shock. Four of these six were treated with antibiotics, steroids and vasopressor agents, one with antibiotics alone and one with antibiotics and steroids. Development of jaundice and/or anuria are bad prognostic signs. It should be added that Case #5, in addition to infection, showed toxic effects to the kidneys from the injection of soap and turpentine via syringe by a criminal abortionist; and Case #9, in addition to gas gangrene infection, showed toxic effects to the kidneys from the injection of a soap solution via plastic tube by a criminal abortionist. In all 10 of these patients, physician care was assessed as adequate. All 10 had autopsies. Since these were self-induced or criminal abortions, all 10 should have been considered preventable with patient responsibility, but the first four were not so considered. They were assessed, instead, as disease responsibility — in the years 1950 through 1953, when the Committee was primarily interested in physician care and was more lenient regarding patient responsibility.

The second group of septic abortions were four patients with spontaneous, incomplete abortions, who became infected (Table 7). Intrauterine and/or blood cultures showed gram-negative organisms in three; blood culture was sterile in one after antibiotic therapy. Three of these presented a primary picture of septic shock. Each was given antibiotics, vasopressors and steroids. Physician care was adequate in all; none was considered preventable.

The last group in the septic abortion category consisted of two patients, each of whom had a nonindicated D & C and who expired from septic shock. Both deaths were considered preventable with physician responsibility. Brief protocols of these follow.

The first was a 16-year-old obese, illegitimately pregnant primigravida, who consulted her physician at six-months gestation because of vaginal bleeding. She did not mention pregnancy, and he failed to make a diagnosis of pregnancy. Instead, he made a diagnosis of functional uterine bleeding and proceeded to do dilatation and curettage. At D & C he was surprised when pieces of fetal foot were obtained

Continued

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*Presented at John L. McKelvey 25th-Year Anniversary Celebration, Oct. 26, 1963.

**Continued from Minnesota Med. August issue, Page 999.

***From the Minnesota Maternal Mortality Committee.

Address for reprints: St. Louis Park Medical Center, 4959 Excelsior Blvd., Minneapolis, Minn. 55416.

and bleeding became profuse. He became frightened and packed the uterus. She expired from septic shock. The patient received inadequate blood replacement therapy, inadequate antibiotic therapy too late, and inadequate consultation. Vasopressors and steroids were given terminally.

The second patient was a 36-year-old para 4 who was admitted to the hospital at 19 weeks gestation as a threatened abortion. The cervix was closed. The physician decided that the case was an inevitable abortion and proceeded with dilatation and curettage. Pieces of placental tissue and umbilical cord were obtained. Profuse bleeding ensued. The physician then discontinued the procedure and packed the uterus. The patient expired from septic shock after having passed the fetus with placenta still in utero. She received no vasopressors and no steroids. The Committee assessed this death as preventable with physician responsibility due to inadequate patient study, no indication for D & C, and once done, failure to completely empty the uterus, inadequate blood replacement, and inadequate antibiotic therapy.

Regarding the management of septic shock, the accepted treatment by most authorities is massive antibiotics, large doses of corticosteroids, fluids, plasma and blood as indicated. The use of vasopressor substances is controversial.

Puerperal Infection

Of the 12 puerperal sepsis deaths, six had intrauterine and/or blood cultures, all of which showed gram-negative organisms (Table 8). The bacteriologic finding is in direct contradiction to the textbook[4] teaching that streptococci are the most frequent offending organism. One wonders whether this is due to the fact that previous antibiotic therapy might have affected the flora or whether, since penicillin is the most frequently used antibiotic, puerperal sepsis cases caused by streptococci recovered, leaving only cases with gram-negative organisms responsible for the deaths.

Nine of these 12 deaths manifested septicemic-shock pictures. Three of these received antibiotics, vasopressors and steroids, three, antibiotics and vasopressors, one, antibiotics and steroids, one, antibiotics alone; and one received no treatment since she died at home. Two of the 12 deaths manifested anuria before death. Time of membrane rupture before delivery is also tabulated in Table 8. Regarding over-all medical care of these 12 patients, the Committee assessed the care as adequate in eight and faulty and contributory to death in four. Two deaths were assessed as preventable with physician responsibility in both. A brief protocol of one of these follows.

TABLE 7
Septic Abortions, 1950-61

Self-Induced Or Criminal	Bacteriology	Shock	Jaundice	Anuria
1	Sterile*	0	Yes	Yes
2	Pseudomonas	0	Yes	Yes
3	E. Coli	Yes	0	0
4	E. Coli & Aerobacter	Yes	0	0
5	E. Coli	0	Yes	Yes
6	E. Coli & Beta hemolytic strep.	0	0	Yes
7	Beta hemolytic strep.	Yes	0	0
8	Clostridium perfringens	Yes	Yes	Yes
9	Clostridium perfringens	Yes	Yes	Yes
10	Clostridium perfringens	Yes	Yes	Yes
Spontaneous Incomplete				
11	E. Coli & Proteus	Yes	0	0
12	Pseudomonas	0	Yes	Yes
13	Sterile*	Yes	0	0
14	E. Coli	Yes	0	0
Nonindicated D & C				
15	None	Yes	0	0
16	None	Yes	0	0

*Blood culture after antibiotics

This patient was a 23-year-old primigravida with a undetected midpelvic contraction. No clinical pelvic mensuration was done. No X-ray pelvimetry was obtained — only anteroposterior and lateral films of the pelvis. After 35 hours of ruptured membranes and 35 hours of obstructed labor (caput of vertex at -1 station), classical cesarean section was carried out. No antibiotics were prescribed during the prolonged, obstructed labor. Postoperatively she developed ileus, peritonitis, and septicemia, and expired on the fifth post-partum day. The Committee assessed the death as preventable on the basis of failure to detect midpelvic contraction (no clinical mensuration or X-ray pelvimetry), delay in starting antibiotic therapy earlier, delivery by classical cesarean section instead of low segment cesarean section, after 35 hours of ruptured membranes and obstructed labor, and inadequate therapy for septic shock.

It is interesting to note that there was one puerperal sepsis death in a patient who had had a previous Shirodkar procedure. She was a 22-year-old para 1-0-3-1, who had had one spontaneous full-term delivery and then three late abortions due to an incompetent cervical os. A Shirodkar procedure, using #1 silk, was done at 20 weeks gestation during current pregnancy. Her postoperative course was uneventful. At 31 weeks gestation her membranes ruptured spontaneously. She was admitted to the hospital, having no contractions and was placed at bed rest. Twelve hours later active labor began. At this time her blood pressure was 80/40, pulse rate 120, and temperature 103°. The suture was cut and intrauterine culture and blood culture showed E. Coli. Adequate treatment was instituted and she delivered spontaneously a 4 lb. 6½ oz. stillborn infant nine hours after the suture was cut. The patient expired three hours post partum in septic shock state.

An unusual case report in this group warrants brief mention. The patient was a 33-year-old para 5 who had had an uneventful pregnancy and delivery. At almost three months post partum she presumed she was pregnant again because she hadn't menstruated since delivery. Some sort of instrumentation was carried out and she was admitted to the hospital in a moribund state from septicemic shock. Adequate therapy was instituted, but she expired soon after admission. Autopsy showed no evidence of a new pregnancy.

Ruptured Appendix

The reasons for including these four ruptured appendicitis deaths in the obstetrical category have already been discussed. Two of these were considered preventable by the Committee with physician responsibility in both. A brief protocol of one of these follows.

This patient was a 21-year-old primigravida. Her prenatal course was uneventful until the 36th week of gestation, at which time she developed nausea and vomiting and pain in the epigastrium. Five hours later the pain shifted to the right lower quadrant. She saw her physician, who made a diagnosis of "abdominal flu," and symptomatic therapy was prescribed. The pain became more severe, and thinking she might be in labor, she went directly to the hospital instead of home as instructed. The nurse recorded a pulse rate of 120 and via the telephone the physician discharged the patient, prescribing Seconal and a cathartic (Petrolagar and mineral oil). She remained in bed at home for the next four days, vomiting and complaining of abdominal pain. The

TABLE 8
Puerperal Infections, 1950-1961

	Bacteriology	Shock	Jaundice	Anuria	Time Of Membrane Rupture Before Delivery
1.	None	0	0	0	At Delivery
2.	None	0	0	0	At Delivery
3.	E. Coli	Yes	0	0	6 hours
4.	None	Yes	0	0	9 days
5.	None	Yes	0	0	15 hours
6.	None	Yes	0	0	At Delivery
7.	None	Yes	0	0	35 hours
8.	E. Coli & Aerobacter	Yes	0	0	10 days
9.	E. Coli & Staph. aureus	Yes	0	0	3½ hours
10.	E. Coli	0	0	Yes	22 hours
11.	E. Coli	Yes	Yes	Yes	At Delivery
12.	E. Coli	Yes	0	0	12 hours

Continued

following day she was brought to the doctor's office again. No tenderness was elicited and she was sent home again. The next day she was brought to the hospital by her relatives, in shock, where she delivered a stillborn infant and died as a result of generalized peritonitis from a ruptured appendix. The Committee considered this death preventable on the basis of inadequate work-up, delay in admission to the hospital, prescribing a laxative, no therapy for the shock and severe dehydration, no consultation, delay in recognition of the peritonitis, no gastric suction for the ileus and inadequate antibiotic therapy.

Summary and Conclusions

An analysis of the obstetric infection deaths from the Minnesota Maternal Mortality Study for the 12-year period, 1950-1961, indicates that:

1. Infection ranked second as a primary cause of death in the obstetric category, surpassed only by hemorrhage.

2. Infection constituted only 10% of the total preventable deaths. Fourteen of the 54 infection deaths were assessed as preventable with physician responsibility in only eight.

3. Pulmonary embolism constituted 41% of the infection deaths with septic abortion 30%, puerperal infection 22% and perforated appendicitis 7%.

4. In the over-all physician care of the fatal pulmonary embolism cases the Committee assessed 17 as adequate and five as faulty and contributory. Only two of these 22 were considered preventable.

5. Of the 16 septic abortion deaths, 10 or 63% were self-induced or criminal abortions. In all 10 of these, the Committee assessed physician care as adequate. Four of the 16 were in patients with spontaneous, incomplete abortions and physician care was adequate in all. The remaining two were in patients who had nonindicated D & C, both of which were considered preventable with physician responsibility.

6. It would seem that in septic shock the accepted treatment by most authorities is massive antibiotics, large doses of corticosteroids, fluids, plasma and blood as indicated. The use of vasopressor substances is controversial.

7. Of the 12 puerperal sepsis deaths, six had intrauterine and/or blood cultures, and all showed gram-negative organisms. This bacteriologic finding is in direct contradiction to the textbook teaching that streptococci are the most frequent, offending organisms.

8. The Committee assessed physician care as adequate in eight of the puerperal sepsis group, and faulty and contributory in four. Two of these were assessed as preventable with physician responsibility.

9. There were four deaths due to ruptured appendicitis and the Committee assessed two as preventable with physician responsibility.

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Conscience is the still small voice that makes you feel still smaller.—Optimist

Author Unidentified

A specialist is a man who knows more and more about less and less until he knows everything about nothing. A general practitioner is one who knows less and less about more and more until he knows nothing about everything.

Special Article

Statewide Screening of Newborn Infants for Phenylketonuria

A. B. ROSENFIELD, M. D.*
Minneapolis, Minnesota

Phenylketonuria (phenylpyruvic oligophrenia, often abbreviated PKU) is an hereditary disease due to a defect in the metabolism of the essential amino acid phenylalanine. In phenylketonuria abnormal amounts of phenylalanine accumulate in the tissues, serum, and body fluids. The infant appears normal at birth, but with the ingestion of protein-containing food the accumulation of phenylalanine and its derivatives affects the development of the central nervous system, usually resulting in severe mental deficiency. Early recognition and treatment with a low phenylalanine diet will prevent this deficiency. (Details of the disease, its recognition and treatment were discussed by Fisch & Davis in the May 1964 issue of Minnesota Medicine, pp. 501-506).

Screening Tests

In 1961, screening of infants for phenylketonuria was begun in the four-county area of Clay, Becker, Wilkin and Ottertail, under the auspices of the Child Development Center for retarded children at Fergus Falls.

Ferric Chloride Test

Packets of material for the testing of a wet diaper or urine by means of 10% ferric chloride were provided to physicians in this area for distribution to mothers of newborns. A stamped envelope was included for return of filter paper to the physician. It was recommended that the procedure be carried out first at four to six weeks of age and three times during the first four months of life at routine medical checkups. Since positive or doubtful urine tests must be confirmed by a blood serum phenylalanine determination to establish a final diagnosis, these confirmatory tests are available to physicians as a service of the medical laboratories of the Minnesota Department of Health. Subsequently, these packets were made available to all hospitals requesting them, and 32 out-state hospitals are currently supplied on a monthly basis.

Phenistix Test

Many hospitals and physicians have been using the Phenistix test for phenylpyruvic oligophrenia testing, a procedure similar to the ferric chloride test. Phenylpyruvic acid is not excreted in large amounts in the urine until the infant is from four to six weeks of age. Thus the urine test is seldom positive before this period and must be carried out in the physi-

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*Director, Division of Special Services, Minnesota Department of Health, University Campus, Minneapolis.

Continued

cian's office after the newborn has been discharged from the hospital. Additional hospitals and a large number of physicians have participated in the ferric chloride screening program, but follow-up is difficult because it requires the active co-operation of the mother as well as the physician, and tests must be repeated.

Guthrie Test

To overcome the problem of infants missed in the ferric chloride screening program, a bacteriologic test for phenylketonuria has been developed by Dr. Robert Guthrie of Buffalo, New York, designed to detect elevated phenylalanine levels in newborn infants before discharge from the hospital. Supposedly, this test would demonstrate elevated phenylalanine blood levels below 20 mg. per 100 ml., i.e., levels at which there is usually insufficiently increased phenylpyruvic acid in the urine detectable by the ferric chloride test. To test this claim, during the past year 32 state health departments have actively participated with more than 600 hospitals in field trials of Guthrie's phenylalanine screening method for the detection of phenylketonuria, sponsored by the U. S. Children's Bureau. In Minnesota the testing was carried out under the auspices of the St. Paul Department of Health.

The Guthrie screening method for phenylketonuria detection will be carried out in the medical laboratories of the Minnesota Department of Health. It is an inhibition assay process in which a drop of blood is collected on special filter paper discs and mailed by the hospital or physician to the state health department medical laboratories.

The discs are cultured with *bacillus subtilis* on a medium containing a growth inhibitor. A halo of growth of the organism surrounding the disc indicates increased phenylalanine content. The width of the halo is measured for per cent concentration. Serum phenylalanine determination for positive diagnosis will then be carried out when necessary so that the physician may institute the appropriate follow-up.

Incidence

Prior to the field trials, the incidence of phenylketonuria was thought to range from one in 20,000 to one in 40,000 live births. Of the 400,000 newborns tested by the Guthrie method there were 40 infants with phenylketonuria. In the 10,901 newborns screened in Minnesota there was one infant with phenylketonuria, an incidence of one to 10,000, or about double the incidence that had been previously estimated.

Although the disease is rare and constitutes only about one per cent of the mentally retarded in institutions, its occurrence at the present time is a needlessly catastrophic event, since it is usually remediable when diagnosed early. Prompt recognition and proper management, including low phenylalanine diet, can prevent the severe mental retardation that is nearly always associated with untreated cases. The Phenistix and ferric chloride tests of the urine, although important, are not reliable under the age of four to six weeks. Since the Guthrie test permits screening while the baby is still in the hospital, diagnosis can be made before the infant escapes medical attention for some unpredictable length of time. Should the baby leave the hospital before the test is done, family physician follow-up for the Guthrie test will become necessary. This procedure will also be necessary if the infant is discharged before the fifth day or the test is made before the infant has been on milk long enough to make the test valid. A repeat test should be done at first post-partum visit.

It is anticipated that other inborn errors of metabolism that cause preventable disease may be included in a battery of screening tests, e.g., galactosemia, maple syrup urine disease, and histidinemia.

State Board of Health Measures

Facilities and staffing have been completed for statewide testing for phenylketonuria by the state health department laboratories. On August 1, 1964, all physicians and hospitals received information about the service, including instructions, kits, and envelopes. A public health nurse consultant in mental retardation will be available to physicians, hospitals, and community agencies in extending services in the field of retardation, especially as they relate to phenylketonuria and other inborn errors of metabolism.

Human-genetics counseling on the inheritance of this disease and the detection of carriers among relatives of affected individuals is available to physicians and to families on a referral basis through the human genetics unit of the state health department. Approximately one child in four will be affected if both parents are carriers of the gene for phenylketonuria. When a child is diagnosed as a phenylketonuric, both parents, two thirds of his normal siblings, and half of his genetically related aunts and uncles will carry a gene for phenylketonuria. These relatives, who are not themselves clinically affected, should know that the inherited trait exists in their families and what the risk of occurrence is in their own offspring.

A study of siblings of phenylketonuric parents is currently in progress in co-operation with Faribault State School and Hospital. A register of this disease and other congenital malformations has been established in the state health department. Laboratory facilities for chromosome analyses and study will be available through the human genetics unit as soon as equipment and staff can be provided.

The detection of phenylketonuria is of special importance to the state health department because it is a practical preventive public health measure. Since more than 99 per cent of Minnesota births occur in hospitals, the hospital is a natural focal point for phenylpyruvic oligophrenia screening. The active co-operation of the physician is necessary for follow-up in his office to supplement the hospital screening program.

The brain is a wonderful organ; it starts working the moment you get up in the morning, and does not stop until you get into the office.—Robert Frost

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I am at the moment deaf in the ears, hoarse in the throat, red in the nose, green in the gills, damp in the eyes, twitchy in the joints and fractious in temper from a most intolerable and oppressive cold.—Charles Dickens

---

Committee: a group of men who keep minutes and waste hours.—H. W. Van Loon

Of 1,028 patients with confirmed respiratory infections... 954 or 92.8% were treated successfully with Signemycin®

Note:
Hammerl* selected his patients for treatment with Signemycin on the basis of demonstrated bacteriological resistance to other antibiotics or failure of previous therapy. Of 100 patients with various respiratory tract infections, 95 responded to Signemycin. Pathogens isolated included staphylococci and *Diplococcus pneumoniae*.

*Hammerl, H.: Wien. Med. Wschr. 108:629, July 26, 1958.

Condition	No. of Patients	No. Cured with Signemycin
Abscess, pulmonary	17	16
Bronchiectasis	19	13
Bronchitis	286	267
Bronchopneumonia	192	179
Empyema	12	11
Pneumonia, lobar	150	146
Pneumonia, other febrile	160	150
Various infected pneumopathies	192	172
Totals	1,028	954 (92.8%)

consistently effective...often when others fail

Signemycin®

tetracycline HCl, 167 mg.; oleandomycin as triacetyloleandomycin, 83 mg.

capsules (250 mg.)

Also available as Syrup, Pediatric Drops, and half-strength Capsules

Brief Summary and Bibliography follow.

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Meetings and Announcements

If you wish to be held in esteem, you must associate only with those who are estimable.—Bruyere

SEPTEMBER

Minnesota Heart Association and Mayo Clinic Symposium on Clinical Applications of Electronics in Cardiovascular Disease, September 10 and 11, Rochester. Contact: J. F. McCally, Secretary, Mayo Clinic, Rochester.

Minnesota Academy of General Practitioners Fall Refresher Course, September 16-17. Leamington Hotel. Contact: W. H. A. Watson, M.D., Midway Medical Building; St. Paul.

Twin Cities Diabetes Association and the Methodist Hospital Annual Symposium "Current Management of Diabetes Mellitus" September 19th at Methodist Hospital. Contact: Donnell D. Etzwiler, M.D.; St. Louis Park Medical Center; 4959 Excelsior Blvd., Minneapolis, Minnesota.

Minnesota Radiological Society Fall Meeting, September 18-20, Ruttger's Pine Beach Lodge, Brainerd. Contact: Frank Anderson, M.D.; Northwestern Hospital in Minneapolis.

American College of Obstetricians and Gynecologists (District 2), Concord Hotel, Lake Kiamesha, N. Y., Sept. 24-27, Exec. Dir: Donald F. Richardson, 79 W. Monroe, Chicago 3.

American Medical Writers' Association, Benjamin Franklin Hotel, Philadelphia, Sept. 25-26. Exec. Sec: James E. Bryan, 2000 P St. NW, Washington, D. C. 20036.

American Roentgen Ray Society, Radisson Hotel, Minneapolis, Sept. 29-Oct. 2. Sec: C. Allen Good, M.D.; Mayo Clinic, Rochester, Minn.

Clinical Orthopaedic Society, Kahler Hotel, Rochester, Minn., Sept. 24-26. Sec-Treas: Joseph E. Brown, M.D.; 10515 Carnegie, Cleveland 6.

Society for Pediatric Radiology, Radisson Hotel, Minneapolis, Sept. 28. Exec Sec: John L. Gwinn, M.D.; Childrens Hospital, 4614 Sunset Blvd, Los Angeles 27.

OCTOBER

Sixteenth Postgraduate Assembly of The Endocrine Society, October 5-9, in Rochester at the Mayo Clinic. Contact: Dr. Edward H. Rynearson of the Mayo Clinic. Registration is $100 and limited to 250.

American Medical Association Second Annual Community Health Week will be observed October 18-24. All media will encourage recognition of the achievements of medicine and public health during this week.

VII International Congress on Diseases of the Chest, October 11-15 in Mexico City. Write: American College of Chest Physicians, 112 East Chestnut Street, Chicago 60611.

Second Annual Fall Meeting of the American College of Physicians, October 8-10, Hotel Biltmore, Los Angeles, California. Info: Edward C. Rosenow, Jr., M.D.; 4200 Pine Street, Philadelphia, Pa.

American Association for Surgery of Trauma, Drake Hotel, Chicago, Oct. 1-3. Sec: Sawnie R. Gaston, M.D.; 180 Ft. Washington Ave., New York 32.

American College of Surgeons, Conrad Hilton Hotel, Chicago, Oct. 5-9, Dir: John P. North, M.D.; 55 E. Erie, Chicago 11.

American Electroencephalographic Society, Bishop's Lodge, Santa Fe, N. M., October. Sec: Kenneth A. Kooi, M.D., University of Michigan Medical Center, Ann Arbor.

ANNOUNCEMENTS

Next scheduled Part I (written) examination of American Board of Obstetrics and Gynecology, will be held December 11 at 2:00 P.M. at various examining centers. Candidates eligible to take test will be notified on or about November. Contact: Clyde L. Randall, M.D.; 100 Meadow Road, Buffalo, New York.

Of 507 patients with confirmed ear, nose and throat infections... 465 or 91.7% were treated successfully with Signemycin®

Note:
Adams,* whose 50 patients included 20 with ENT infections, stated that Signemycin "was particularly valuable in infections that did not respond to other antimicrobial agents, and in patients to whom penicillin could not be given." All his cases responded within five days; in most patients, all signs of infection disappeared in three days.

*Adams, J.: J. Tenn. Med. Ass. 50.446, Nov., 1957.

Condition	No. of Patients	No. Cured with Signemycin
Otitis media	90	86
Pharyngitis and laryngitis	162	148
Sinusitis	68	55
Tonsillitis and peritonsillitis	163	153
Various	24	23
Totals	507	465 (91.7%)

consistently effective...often when others fail

Signemycin®

tetracycline HCl, 167 mg.; oleandomycin as triacetyloleandomycin, 83 mg.

capsules (250 mg.)

Also available as Syrup, Pediatric Drops, and half-strength Capsules

Brief Summary and Bibliography follow.

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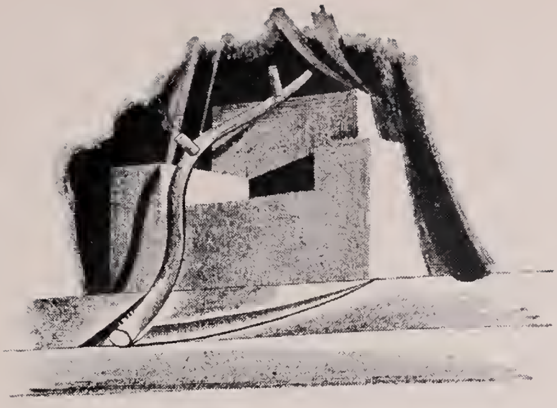

In Memoriam

Is death the last sleep? No, it is the last and final awakening.—Walter Scott

LEONARD K. BUZZELLE

Dr. Leonard K. Buzzelle, 63, Minneapolis surgeon, died June 23rd. He was a native of Seattle, Washington, but graduated from the University of Minnesota Medical School in 1927.

He was a member of the Hennepin County Medical Society, American College of Surgeons, Minnesota State Medical Association and American Medical Association.

He is survived by his wife, daughter and son.

CHARLES E. GOODMAN

Dr. Charles E. Goodman, 79, Virginia physician, died July 19. He was born in Russia and obtained his medical degree from the Northwestern University Medical School at Chicago. He went to Virginia in 1914 and practiced medicine there until his demise. He was school district physician of Virginia for thirty-six years.

Dr. Goodman was a Life and 50 Club member of the Minnesota State Medical Association, a member of the Range Medical Society and the American Medical Association.

ROLLA I. STEWART

Dr. Rolla I. Stewart, 71, Minneapolis surgeon, died June 8. He was born at Hannibal, Missouri, and received his medical education at the Universities of Missouri and Minnesota.

Dr. Stewart was a member of the American College of Surgeons, Hennepin County Medical Society, the Minnesota State Medical Association, American Medical Association, Business and Professional Men's Post of the American Legion, A.F.&A.M. Scottish Rite, Zuhrah Temple and Phi Beta Pi fraternity.

He is survived by his wife, a son and a daughter.

MILTON M. BALCOME

Dr. Milton M. Balcome, 57, St. Paul physician, died June 20th following a heart attack. He was born at St. Paul and received his medical degree from the University of Minnesota.

Dr. Balcome was a member of the Ramsey Medical Society, Minnesota State Medical Association and the American Medical Association.

He is survived by his two daughters.

WILLIAM E. HALL

Dr. William E. Hall, 52, St. Paul physician, died May 31 of a heart attack. Dr. Hall graduated from Macalester college and Marquette university medical school and started the practice of medicine at Maple Lake, in 1946.

He was born at St. Columb Minor, England, and was a member of the American Association of General Practitioners, Ramsey County Medical Society, Minnesota State Medical Association and the American Medical Association.

He is survived by his wife and a son.

LOWELL M. CAMPBELL

Dr. Lowell M. Campbell, 78, Edina village health officer for twenty-five years, died June 1, following a month's illness. He was born at Miller, South Dakota, and graduated from the Rush Medical School in Chicago.

He was a member of the Hennepin County Medical Society, a 50 Club and life member of the Minnesota State Medical Association and a member of the American Medical Association. He was a staff doctor at Northwestern hospital for fifty years.

Dr. Campbell is survived by his wife and two sons.

Of 1,021 children with various confirmed infections... 950 or 93.0% were treated successfully with Signemycin®

Note:
The effectiveness of Signemycin was demonstrated by Chattas and his co-workers* who administered Signemycin to 30 children with serious staphylococcal infections resistant to commonly used antibiotics. Only one failed to respond. In each case the use of this drug was indicated by antibiogram. Those children treated with a nonselected antibiotic—for comparative purposes—took three times longer to recover.

Chattas, A. et al.: Antibiot. Med. 7:300, May, 1960.

Condition	No. of Patients	No. Cured with Signemycin
Eye, ear, nose, throat infections	368	343
Respiratory infections	369	346
Gastrointestinal infections	42	30
Skin and soft-tissue infections	38	37
Deep-seated or generalized infections	47	44
Various conditions	157	150
Totals	1,021	950 (93.0%)

consistently effective...often when others fail

Signemycin®

tetracycline HCl, 167 mg.; oleandomycin as triacetyloleandomycin, 83 mg.

capsules (250 mg.)

Signemycin is also available as half-strength Capsules, preconstituted raspberry-flavored Syrup and Pediatric Drops

Brief Summary and Bibliography follow.

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FREDERICK A. OLSON

Dr. Frederick A. Olson, 80, of Pomona, California, died July 10th. Before his retirement, Dr. Olson practiced medicine in Minneapolis and Los Angeles. He was a native of Wells, studied at the University of Minnesota, the Rush Medical School of the University of Chicago and the Mayo Clinic.

Dr. Olson was a former president of the Minneapolis Society of Surgeons and was a founder of the American Board of Surgery. He was also a member of the American Medical Association.

He had no immediate survivors.

SAMUEL JOSEPH HILLIS

Dr. Samuel Hillis, 83, former resident of St. Paul who practiced medicine in Minneapolis for many years, died at Bradenton, Florida, June 27th. He was born at Hanover, Canada, and was a graduate of the Toronto University Medical School.

Dr. Hillis served during both world wars in the Army Medical Corps, was a member of the Masonic Lodge, the American Legion, Hennepin County Medical Society, the American Medical Association, and a life and 50 Club member of the Minnesota State Medical Association.

He is survived by his wife, two daughters and two sons.

ALLAN J. HILL, JR.

Dr. Allan J. Hill, Jr., 49, formerly of Minneapolis, died July 25, at Portola Valley, California. He was born in Minneapolis and graduated from the University of Minnesota Medical School. He practiced medicine with Dr. Erling Platou in Minneapolis.

Dr. Hill was head of the Pediatrics Department of the University of Oregon. He had been an instructor at Tulane University, New Orleans, and an associate professor at Lying-in Hospital in Chicago. He was a member of the American Medical Association.

He is survived by his wife, two daughters and two sons.

EDWARD A. EBERLIN

Dr. Edward A. Eberlin, 86, one of the state's oldest practicing physicians, died July 25th. He was born at Blue Earth, Minnesota, and practiced medicine in that community for sixty-two years. His medical degree was obtained from the University of Minnesota.

He was a member of the West Central Medical Society, and a 50 Club and life member of the Minnesota State Medical Association, and a member of the American Medical Association.

He is survived by his wife and a daughter.

MYRON J. HERTZ

Dr. Myron J. Hertz, 52, St. Paul surgeon, was killed in a crash involving two cars and a truck, on August 6th. He was on a house call, and his car collided with a dump truck at Maplewood.

He was born at St. Paul and graduated from the University of Minnesota Medical School. He was a member of the American Academy of General Practitioners, Ramsey County Medical Society, Minnesota State Medical Association, and American Medical Association and was on the staff of St. Luke's hospital. He had been a city and county physician since 1940.

He is survived by his sister.

ANDREW S. ARNQUIST

Dr. Andrew S. Arnquist, 66, St. Paul ENT doctor, died August 14th after a long illness. Born in New Richmond, Wisconsin, Dr. Arnquist received his medical degree from the Illinois medical school in Chicago.

He was a member of the New Richmond Masonic lodge, Ramsey County Medical Society, Minnesota State Medical Association, and a member of the American Medical Association.

He is survived by his wife and two sons.

ARTHUR PLANKERS

Dr. Arthur G. Plankers, 75, of Dubuque, Iowa, a graduate of the University of Minnesota School of Medicine, died August 10th.

He had a teaching fellowship at the University of Minnesota in 1921, and in 1922 was a fellow in surgery at the Mayo Clinic. He went to Dubuque in 1926 as surgeon with the Medical Associates of Dubuque. Dr. Plankers was a member of the Iowa Medical Society, American Medical Association and a fellow in the American College of Surgeons.

He is survived by his sister and two brothers.

LAWRENCE O. DOYLE

Dr. Larry O. Doyle, 71, Minneapolis physician and surgeon for 42 years, died at his home, August 11th. He was born at Plankington, South Dakota, and graduated from the University of Minnesota medical school.

He was a former member of the Minnesota football squad and served as the team's physician when he returned from World War I. Dr. Doyle was a former chief of staff at St. Mary's hospital, a fellow of the American College of Surgeons, member of the Hennepin County Medical Association, Minnesota State Medical Association, and American Medical Association.

He is survived by his wife, three daughters and four sons, two of whom are Dr. Larry O. Doyle, Jr. of Wayzata and Dr. Owen P. Doyle of San Francisco.

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SIGNEMYCIN®

Side Effects: Glossitis and allergic reactions, as well as severe anaphylactoid reactions, have been reported as rare side effects. Should significant reaction or idiosyncrasy occur, discontinue medication and institute countermeasures. Use of tetracycline during the last trimester of pregnancy, neonatal period and early childhood may cause discoloration of developing teeth. Reduce usual oral dosage and consider serum level determinations in patients with impaired renal function to prevent possible liver toxicity due to excessive accumulation of antibiotic in the serum.

Precautions: Overgrowth of nonsusceptible organisms may occur. In such cases, discontinue medication and institute appropriate specific therapy as indicated by susceptibility testing. Aluminum hydroxide gel given with antibiotics has been shown to decrease their absorption and is contraindicated. The coloring agents used in Signemycin Syrup and Pediatric Drops may produce red discoloration of stools.

Triacetyloleandomycin, a constituent of Signemycin, administered to adults in daily oral doses of 1.0 Gm. (3 Gm. Signemycin) for periods of more than ten days may produce hepatic dysfunction and jaundice. In the rare patient who requires this high dosage level of Signemycin initially, liver function should be carefully followed and dosage should be reduced, as promptly as possible, to the usual recommended range of 1.0 to 2.0 Gm. per day. Therefore, Signemycin is recommended primarily for the treatment of acute or severe infections, with treatment restricted to a ten-day period. If clinical judgment dictates continuation of therapy beyond ten days, serial monitoring of the liver profile should be carried out, including BSP, transaminase, and cephalin flocculation tests. Changes observed in liver function were reversible following discontinuation of the drug.

Formulas: Capsules: 250 mg. Signemycin (167 mg. tetracycline HCl and 83 mg. oleandomycin as triacetyloleandomycin).

Capsules: 125 mg. Signemycin (83 mg. tetracycline HCl and 42 mg. oleandomycin as triacetyloleandomycin).

Syrup: 125 mg. Signemycin (tetracycline equivalent to 83 mg. tetracycline HCl and 42 mg. oleandomycin as triacetyloleandomycin) per 5 cc.

Pediatric Drops: 100 mg. Signemycin (tetracycline equivalent to 67 mg. tetracycline HCl and 33 mg. oleandomycin as triacetyloleandomycin) per cc.

More detailed professional information available on request.

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Of 5,057 patients with confirmed infections of all body systems... 4,731 or 93.5% were treated successfully with Signemycin®

Note:

The high rate of response to Signemycin in these cases is noteworthy because the totals include many patients with difficult-to-treat infections, many whose infections had proved resistant to other agents, and many who had been treatment failures on other therapy.[1-87] In addition the following criteria were used for the cases cited: (1) only published results were used (2) results were confirmed by clinical and/or laboratory findings (3) patients were cured, not "improved" (4) dosage conformed with current recommendations in the United States (5) no other anti-infective agents were used concomitantly (6) no instance of prophylactic use was included in these tabulations.

Condition	No. of Patients	No. Cured with Signemycin
Ear, nose and throat infections	507	465
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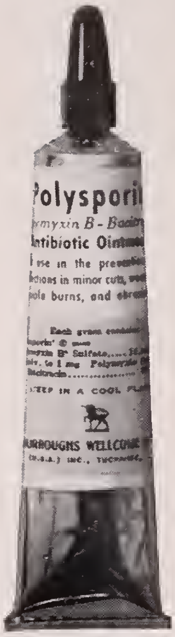

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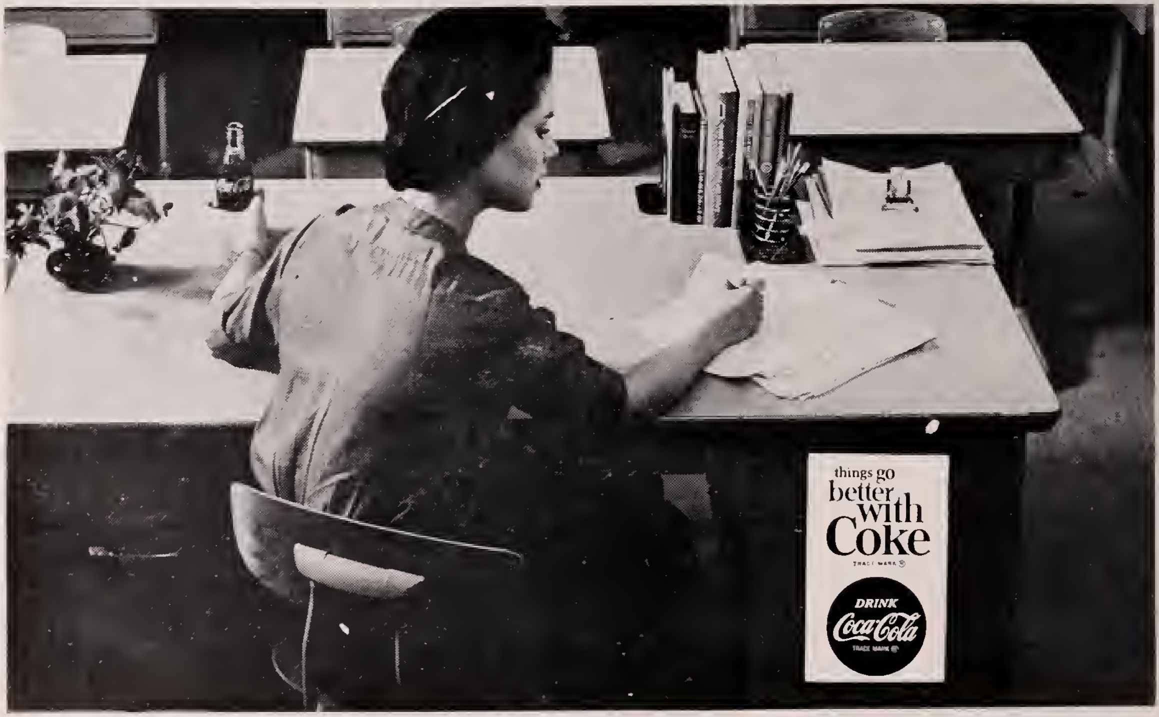
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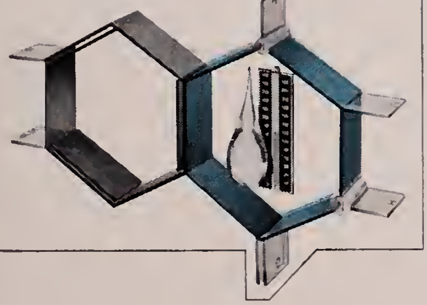

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CONTRAINDICATION: Anuria.

1. Steigmann, F., and Griffin, R.: Evaluation of Quinethazone, a New Diuretic. J. Amer. Geriat. Soc. 11:945 (Oct.) 1963.

2. Schwartz, M.: Office Evaluation of a New Diuretic in Patients with Hypertensive Diseases. Scientific Exhibit Presented at the Clinical Meeting of the American Medical Association, Los Angeles, California, Nov. 25-28, 1962.

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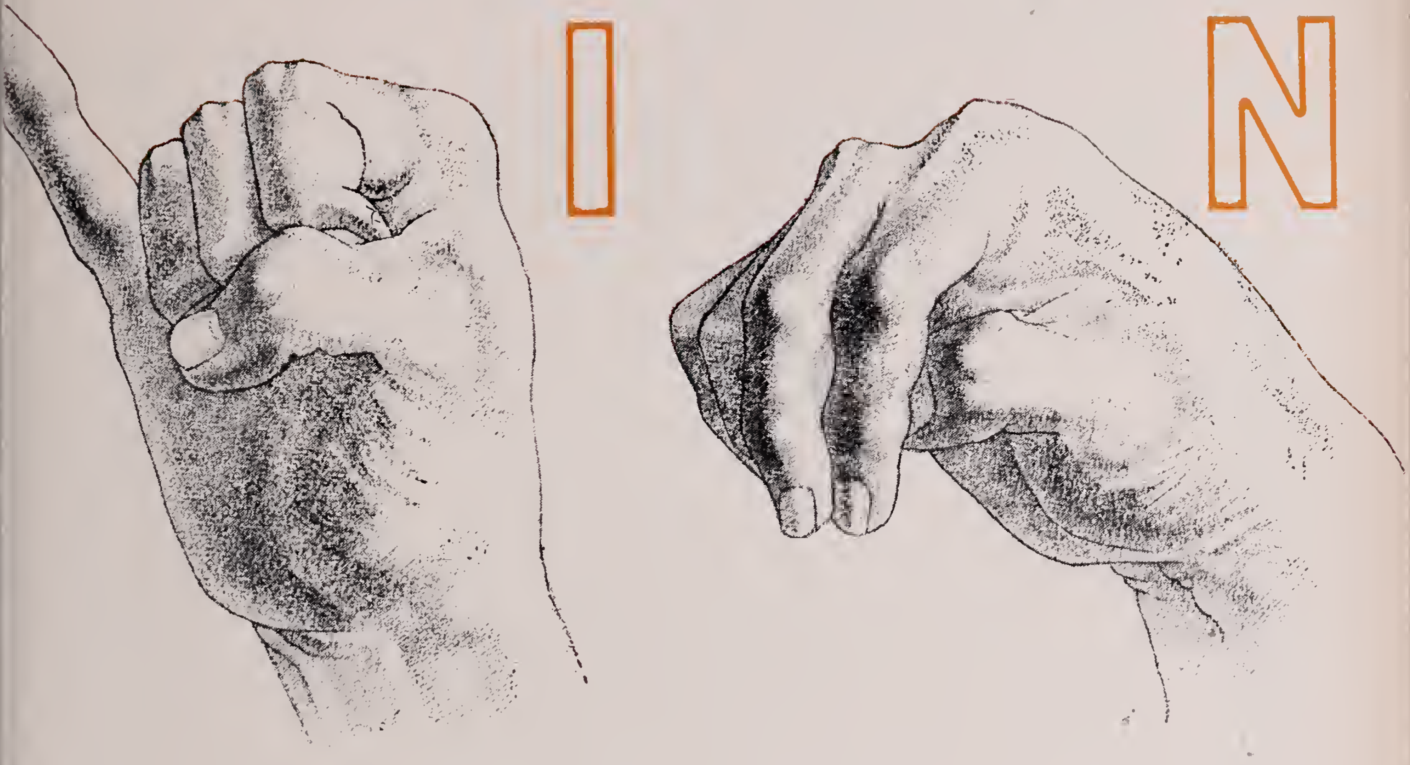

jouty arthritis, rheumatoid spondylitis, osteoarhritis, bursitis, fibrositis, and neuritis. Arthralgen nay be used for analgesia in colds, flu, and arious myalgias.

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*Cohen, et al: J.A.M.A., 165:225, 1957.

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History of Medicine

Origins and Development of the Mayo Foundation

VICTOR JOHNSON, M.D., Ph.D.*
Rochester, Minnesota

EVERY LEADING medical center, whether a medical school, a major hospital, or a large clinic, pursues three objectives: namely, medical care of the people, advancement of knowledge through scientific investigation, and the education of physicians. A medical center not dedicated to this threefold objective imposes limitations upon its greatness. The Mayo medical center is best known for the care of the sick, but it would not be great without a devotion to research and education as well.

Many are unaware of the magnitude of our training program; it is probably the largest program of advanced medical education in the world. Our graduate school has an enrollment of more than 600. Almost all of these are physicians. They are medical school graduates, they have served internships, they are licensed to practice medicine. They are in training to become specialists in the various areas of medicine and surgery. Training for specialty practice is carried out on a grand scale, numerically, in this country. Today, more than 1400 institutions are engaged in such residency training, involving nearly 30,000 physicians, almost equaling in number the total count of undergraduate medical students (31,000) in our 83 medical schools. Of these 30,000 residents, two per cent are in Rochester, the remainder in the other 1400 training hospitals of the country.

Beginnings

What were the beginnings of this major educational enterprise? They were small, as were the beginnings of the Mayo Clinic, or of most large undertakings. In one sense, education began here in the 1880s when Will and Charlie returned from medical school to work with, but also to learn from, their father. As additional physicians joined the Mayos in practice, they attracted still others as students, reaching the modest number of 36 by 1912.

The desire, the need to teach, is as old as the profession of medicine. The Hippocratic oath of antiquity admonishes the physician not only to care well for his patients, but to teach the art and practice of medicine to the young, who are also aspiring to become physicians. In no other profession is the urge to teach more compelling than in medicine. In truth, the very word "doctor" means "teacher."

The early teaching at the clinic was informal, largely on-the-job apprentice training, without academic orientation. But soon this approach was

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*Director, Mayo Foundation for Medical Education and Research.

Continued

radically changed through the vision and wisdom of the Mayos and the University of Minnesota authorities, with the establishment of the Mayo Foundation, whose 50th year we now celebrate.

The Mayo Foundation

By 1915, there had occurred a revolutionary advancement in undergraduate medical school education. The American Medical Association, collaborating with the Carnegie Foundation, had markedly improved medical education in the entire country. The co-operative studies of medical schools and the famous "Flexner Report" resulted in a strengthening of the good schools, the consolidation of weak schools into fewer strong institutions, and the elimination of many poor unsalvable schools not worthy of the name.

But in the face of these important improvements in the medical schools, training beyond medical school was in a sad state. Existing facilities for advanced training were entirely inadequate, the demand by physicians for a high quality of such education was not being met, proprietary and "postgraduate" schools of doubtful character were too plentiful, and there was lack of widespread interest in this field of education on the part of medical schools.

In this setting, well-ordered, well-planned comprehensive graduate medical education was established in Rochester and in Minneapolis under the general direction of the Graduate School of the University. Will Mayo, who was then a regent of the University, joined with Guy Stanton Ford, Dean of the Graduate School, in formulating the project.

In essence Doctor Will said, "In Rochester we have all the essential components of a superior educational endeavor in medicine. We have excellent patient facilities in our hospitals and clinics; we have well-equipped laboratories; most important, we have outstanding clinical and scientific talent on the staff. Let us incorporate these educational assets into the University's Graduate School under the name of the Mayo Foundation for Medical Education and Research. Let us establish together, in Rochester and in the University Hospitals, a sorely needed, almost unprecedented program for the training of specialists in the various fields of medicine and surgery." The proposals of Mayo and Ford came to fruition in 1915.

The Academic Degree

It is significant that the plan was oriented toward more than purely professional competence, more than expertness as a practicing surgeon or internist. The aim was to include an improved understanding of the experimental sciences by assignments of students to such laboratories as physiology or biochemistry, and also to inculcate a better appreciation of how scientific truth is discovered by strongly encouraging actual participation in research.

This educational complex was incorporated into an academic degree program. The total three-year educational experience, then unique in the country, included work with patients, laboratory study, research, preparation of a thesis, and written and oral examinations, culminating in a University of Minnesota M.S. or Ph.D. degree.

Another unique feature of the program of education and research was its financing, under policies developed even before the Mayo Foundation was organized. It started as the Mayo brothers became successful. They were very successful medically in the care of patients; they were successful scientifically, in their practical and applied investigations; also, they were successful financially. They and their early associates decided to place themselves on a definite salary, including insurance and annuity provisions. They decided that any income in excess of their salary and other expenses of operation should be returned to the people whence it originated. The best way to accomplish this, it was decided, would be to employ the excess funds for education and research with a view to improved medical care of the people in the future.

This policy, adopted more than a half century ago, has functioned ever since. Proceeds above expenses are still employed for education and research, partly through the Mayo Foundation. An internist or a surgeon on today's Mayo Clinic staff and Mayo Foundation teaching faculty is willing to have a part of what he earns employed for research and for the education of graduate students.

The Mayo Foundation Fellow

The typical fellow of the Mayo Foundation is 27 years old. He has spent four years in college at Columbia or Stanford and four more in medical school in Florida or Oregon. He has interned a year at Massachusetts General or Los Angeles County Hospital. He comes to Rochester after nine or more years beyond high school, depending upon whether he has had additional training, some medical practice, or military service.

He and his wife and child live on a modest stipend. He will be here three to five years before starting practice somewhere in the United States, Canada, or elsewhere on any continent you might name except Antarctica. He becomes a specialist in one of twenty fields of medicine or surgery.

Identification of Specialists

The Mayo Foundation and University of Minnesota degree program accomplished another purpose besides training specialists. It identified them. It provided a means for the public and the medical profession at large to know who are specialists, who are adequately trained as competent surgeons or internists.

The identification of physicians possessing proper basic medical school training had been freely available for many years. Possession of an M.D. degree from an accredited medical school attested to adequate training. The certificate of a state licensing body gave legal recognition of competence.

No such definite objective evidence of specialty training existed. An M.D. could become a specialist by experience in practice, by watching a surgeon in Vienna or Berlin for six months, or by asserting, "I am a specialist."

The Mayo and University degree program sought and achieved a legitimate identification. The M.S. degree, a tangible sheepskin which could be displayed, took its place alongside the medical school's M.D. degree and the state license, certifying to specialty competence. This Minnesota specialty certification program anticipated a nationwide identification plan which is now well established. Today's universally recognized certifi-

Continued

cates of some 20 American Boards in various specialties now fulfill a real national need which was anticipated and met in a limited way by the M.S. degree of the Mayo Foundation and the University.

The Rochester Hospitals

The education of a specialist is impossible without the training and experience provided in hospitals. The Mayo Clinic is primarily diagnostic, and the affiliated hospitals — St. Marys and Methodist — are mainly therapeutic, in which medical and surgical treatment occurs. Although the clinic and the hospitals are under independent ownership and administration, they co-operate in patient care, in education and in research, with an understanding and unity of purpose that are the envy of many a medical center in this country.

Mayo Foundation Today

The aim of providing the best in advanced medical education remains our goal today. The present fellows of the Mayo Foundation are graduate students of the University of Minnesota. The staff of the Mayo Clinic is the faculty of the Mayo Foundation; these physicians, busy in the practice of medicine, take their time and effort and energy to teach fellows. This they do, not because it is expected of them as a duty, but because they demand the opportunity. With no one to teach, many of our staff would leave us. The inquiring mind of the student sharpens the wits of the teacher in his study and management of patients. The give-and-take between student and professor, the interplay between the practice of medicine and the teaching of eager minds stimulates and enriches the life and work of the staff members.

Our alumni — 4000 in number — are carrying on practice in the specialties of medicine and surgery all over the United States and Canada and in 50 countries abroad. With these alumni, the definition "doctor means teacher" still obtains. About 40 per cent of our alumni are on medical school or university faculties throughout this country and the world. Many are full-time faculty members, some are medical school deans, and others are heads of departments. In dermatology, for example, we have provided the present heads of departments at Creighton, Oregon, Stanford and Harvard. Among more than 23,000 part-time medical school clinical teachers, there are more Mayo alumni than physicians from any other advanced training institution in the country.

So, our Mayo enterprise improves health today by providing a superior grade of medicine, and seeks through research and education to improve the health of people of the future. Our students of today become the teachers of tomorrow.

The Mayo Foundation is part of a great university, and as such, the Mayo Foundation must share in what is expected of a university. In the last analysis, the social responsibilities of a university, besides enriching the lives of individual students, can be reduced to two: to train men and women to do the world's work and to advance knowledge through research. These will continue to be the goals in the next 50 years of the Mayo Foundation.

Great men are rarely isolated mountain peaks; they are the summits of ranges.

—T. W. Higginson

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Volume 47

Number 10

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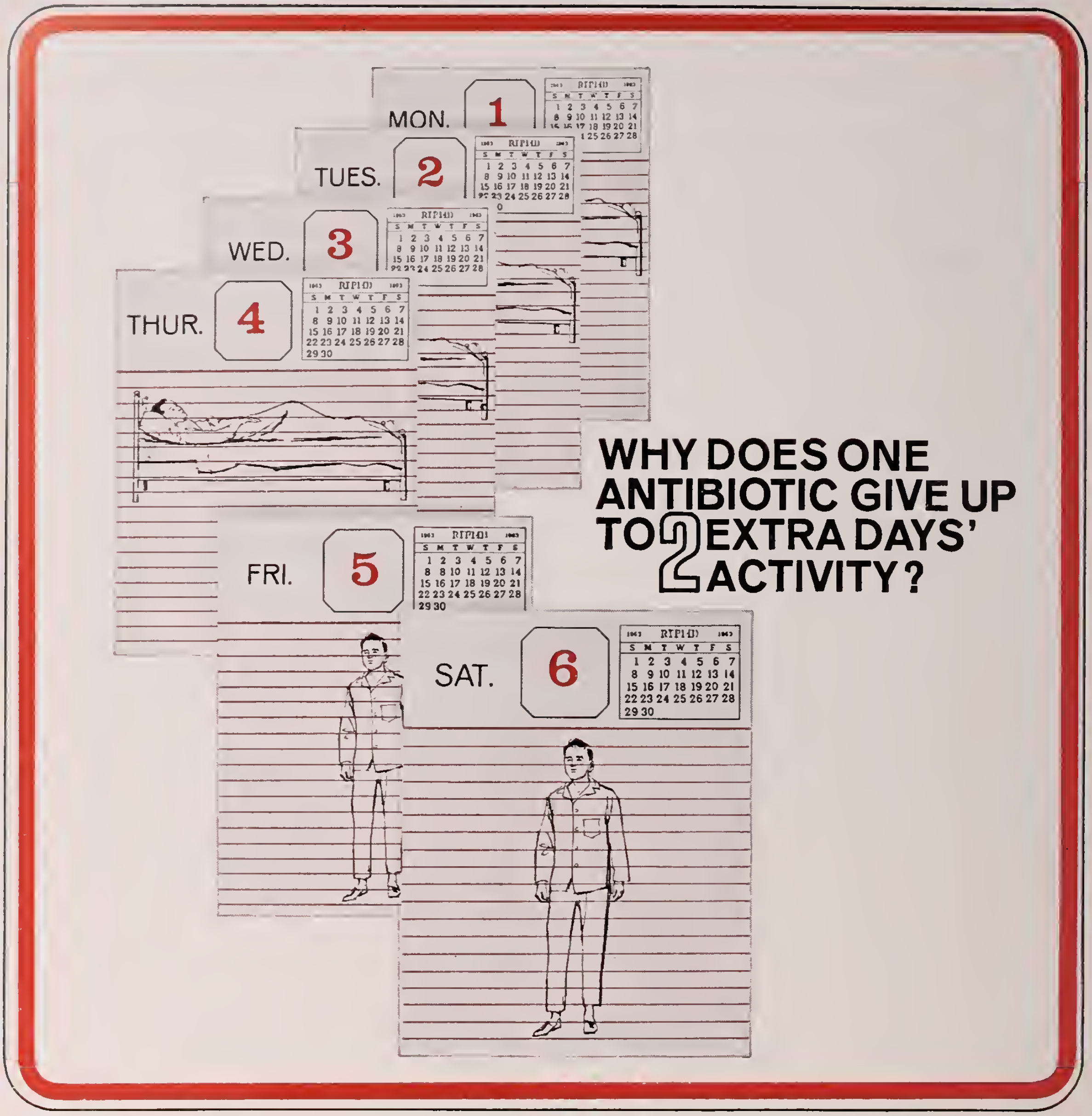
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President's Letter

Arthur Dean Bevan was Professor and Chairman of the Department of Surgery at Rush Medical College of the University of Chicago in 1929. That was the year that the great institution in which he held that important post saw fit to turn me loose on the public — but with reservations. That was also the year that the boy wonder, Robert Hutchins, presided at the graduation ceremony for the first time as President of the University, in the new Chapel at the University. Degrees were granted right and left — doctor's degrees, master's degrees, bachelor's degrees. Those of us who had completed four years in the medical school (the majority of us already held one or more of the degrees just mentioned) were presented, however, with certificates of our achievement. I still wonder how, on that hot, unairconditioned afternoon each of us was handed the proper scroll. Everything came out right though, even to the Home Ec. major who became a Ph. D. by virtue of a thesis on "A Comparison of Three Methods of Washing Dishes." But, I stray from my topic. I have mentioned Dr. Bevan, and medical school certificates given with reservations.

Dr. Bevan, who must have been a very young man at the time, became the first Chairman of the newly established Council on Medical Education in 1904. It is interesting to note that over the years the Council came to be known as the Council on Medical Education and Hospitals but has now recently been restored to its original title. I am sorry that in my naivete when in medical school I recognized Dr. Bevan only as a marvelous surgeon. I now realize that marvelous surgeons were plentiful, but that the Council which he headed was responsible for initiating events which led to the evaluation of medical education culminating in 1910, by publication of the famed Flexner report. At about that time there were 131 medical schools, 21,000 medical students and 4,400 graduates. Certainly, reform was indicated. Dr. Bevan's Council in 1905, had recommended a five year medical course (after the candidate met qualifications adequate for matriculation into a recognized university) to include basic sciences, laboratory sciences and clinical branches, *plus* a sixth year as an intern in a hospital.

After the Flexner report medical school standards were raised to desirable levels. Internships became almost compulsory. By 1915, the University of Minnesota became the first school to require an internship as a degree requirement. Seventeen states demanded proof of internship for licensure. It soon became apparent that a year of internship in "a" hospital might be not what it seemed. So standards for internships, "Essentials of an Approved Internship," were adopted by the Council late in the second decade of this century. Thus it was that the roaring 20's opened with 83 medical schools, 14,500 medical students, 3,200 graduates and 3,000 approved internships. Now, after many turns of the wheel, the situation is as follows: 87 medical schools, 31,500 medical stu-

Continued on Page 1248

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Hemochromatosis

To
the
Memory
of
Dr. Bell

C. J. WATSON, M.D.*
M. J. MURRAY, M.D.*
Minneapolis, Minnesota

SEVEN YEARS after E. T. Bell became emeritus Professor, he made an important contribution on hemochromatosis, a subject in which he had become increasingly interested as a sequel to his interest in diabetes. This study[2] concerned the frequency and degree of hemosiderosis of the liver and diabetes in patients with portal cirrhosis.

History

In the history of hemochromatosis there are several important landmarks: 1. The classical descriptions, extending from 1865-1889, including v. Recklinghausen's introduction of the name, in the latter year.[35] 2. The early recognition by Gilbert[3] that hemochromatosis may be associated with alcoholism. 3. The detailed study by Sheldon in 1935.[39] 4. The recognition that the classical triad of hemochromatosis, pigmentation, diabetes, and cirrhosis may be observed in patients suffering from chronic anemia, with or without multiple blood transfusions.[2] 5. The recognition of latent cases among the family members of patients with typical hemochromatosis, by means of serum iron and liver biopsy iron determinations; also the characteristic increased hepatic uptake of Fe^{59} in such individuals. 6. The recent recognition that portacaval shunting in the human being and experimental animal is often followed by hepatic hemosiderosis, often sufficiently marked to give rise to confusion with hemochromatosis.

Although v. Recklinghausen named the disease and delineated its two principal pigments, there had been clear, prior recognition of the same condition by several of the great French clinicians of the 19th century. Sheldon[39] gives Trousseau (1865) the credit for description of the first "undoubted" case, although he did not propose a name. Six years later Troisier described a second case, emphasizing the association of pigmentary cirrhosis and diabetes mellitus: "La cirrhose pigmentaire dans le diabéte sucré." The next principal contributions were by Hanot and his students. Hanot is known chiefly for his work on an entirely different form of cirrhosis — idiopathic biliary or cholangiolitic cirrhosis. The paper by Hanot and Chauffard was entitled "La Cirrhose hypertrophique pigmentaire dans le diabéte sucré" (1882). In the second paper Hanot and Schachmann introduced the term "bronze diabetes" (1886). In 1889 v. Recklinghausen's well known papers appeared, in which he proposed the term "Hämochromatose" and suggested that the pigmentation was due to the iron-containing "hemosiderin" and the iron-free "hemofuscin."[35]

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*From the Dept. of Medicine, University of Minnesota Hospital.

Another of the great French clinicians of this period, A. Gilbert, perhaps best known for his description of "simple familial cholemia" (constitutional hepatic dysfunction or Gilbert's disease), first pointed out the concurrence of hemochromatosis and alcoholic cirrhosis. This was discussed with his student, Grenet, in two papers, both in 1896 and both entitled "La Cirrhose alcoolique hypertrophique pigmentaire."[12]

Increased Iron Retention

Sheldon collected 345 cases from the literature up to 1935, which he regarded as acceptable examples, and he believed that the disease was probably congenital and familial, an "inborn error of metabolism." He was impressed with the familial incidence of which the literature already provided much evidence, and he concluded that the abnormal iron retention (sic!) began very early in life, quite possibly at or shortly after birth. Only on this basis could he reconcile the finding of 40-50 gm. of iron in the body at age 50 with the studies of hemochromatosis by Dry,[8] which failed to reveal an imbalance between excretion and absorption of iron. Sheldon calculated that a "retention" of as little as 1.25 mg./d., starting early in life would result in the large amounts found in late middle life. He believed that an abnormal avidity for iron of tissues such as liver and pancreas was the "inborn error." Little or no attention was given to the possibility that increased absorption was the primary abnormality. Although in this general period there was belief in increased retention and avidity of cells for iron, without increased absorption, it was recognized that these patients seldom were anemic and then not more than mildly so. Sheldon calculated that with an active accumulation from birth of 1.25 mg./d., at a total intake of 8-10 mg./d., there would still be enough iron available for normal hemoglobin formation.

Refractory Anemia

At the time of Sheldon's work and for some years later, there was no recognition that outspoken hemosiderosis, even with the classical triad of hemochromatosis, might occur as a result of long-standing severe anemia. Dr. Bell's paper includes discussion of cases of this type with and without multiple blood transfusions. Cases of refractory anemia have often been given iron for long periods, but unless the hemoglobin concentration of the red cells is significantly reduced, iron will be without value and may even prove harmful. This also applies to certain hypochromic anemias. The absorption of dietary iron is increased in chronic anemia,[11] and if the iron is not used, it accumulates in the tissues, with possible development of hemochromatosis differing only in pathogenesis from the classical form. This has been noted especially in chronic anemias associated with disturbance of hemoglobin synthesis such as thalassemia and Heilmeyer's sideroachrestic and sideroblastic anemias, which represent hypochromic anemias due to faulty utilization of iron rather than deficiency. The term "sideroachrestic" is used in the sense of Heilmeyer: a faulty utilization of iron in hemoglobin synthesis. The term could also apply to an otherwise normal situation in which large excesses of iron are absorbed in relation to the need of iron for hemoglobin synthesis. Thus hemochromatosis may develop in cases of chronic hemolytic anemia in which iron is administered inadvisedly over long periods.[34] These could scarcely be designated as "sideroachrestic," since, though the utilization of iron for hemoglobin synthesis is highly efficient, yet the amounts absorbed are in excess of this use.

Hemochromatosis

Hemochromatosis has also been associated with megaloblastic anemia, by Kozewski,[26] but all of his nine cases were alcoholics with cirrhosis; and it appears more likely that the megaloblastic anemia was due to folic acid deficiency, and the hemochromatosis to alcoholism and malnutrition (see below).

There has been an unfortunate tendency to confuse the secondary "chronic anemic" form of hemochromatosis with the primary classical type for which there is clear evidence of an inborn error of metabolism. Chronic anemia regularly precedes the secondary form but is seldom observed with the primary classical type, and then only as a late event related to the liver disease. Other secondary forms of hemochromatosis exist in which anemia is more prominent but clearly dependent on serious hepatic disease.

Alcoholism and Nutritional Deficiency

Gilbert and Grenet[12] spoke of alcoholic cirrhosis which was also hypertrophic and pigmentary, thus raising important questions. In brief these questions are:

1. Does hemochromatosis in the chronic alcoholic represent a coincidence of two diseases?

2. Do the states of chronic alcoholism, their attendant dietary deficiency, and/or the resulting Laennec's cirrhosis cause hemochromatosis?

3. Is this in fact the basis of all hemochromatosis other than the "chronic anemic" type? In other words, is hemochromatosis purely an acquired disease and in no sense a genetic or familial abnormality?

These are difficult questions and many students of the disease over the past three quarters of a century have striven to answer them with but indifferent success. The general concept representing the affirmative to questions 2 and 3, is by no means a new one. The belief that portal cirrhosis is the cause of hemochromatosis was first expressed by Simmonds in 1909 and had gained a number in 1935. Sheldon gave careful consideration to the literature but did not accept this view of adherents by the time of Sheldon's review himself. Successive generations of pathologists at the Boston City Hospital have considered that hemochromatosis is an acquired disease, and the present representatives are strong supporters of Simmonds' idea. Hemochromatosis, at least in the broad sense, is of relatively common occurrence in the Boston City Hospital; thus it is understandable that it should have stimulated considerable study over many years. It may also be emphasized that alcoholism, dietary deficiency, and alcoholic-nutritional cirrhosis form a remarkably large segment of the hospital population and that this must be given due attention in considering the results of studies in that institution. A comparison of some recent data reported from this hospital by Pechet and MacDonald[33] with Dr. Bell's results is of considerable interest. The former workers state that idiopathic hemochromatosis is common at the Boston City Hospital, while Dr. Bell emphasizes the rarity of bronze diabetes, only 11 cases with the complete syndrome having been found in 932 cases of clinical portal cirrhosis from the autopsy service of the University of Minnesota between 1911 and 1953. Some degree of hemosiderosis of the liver was observed in 225 of these cases, but in many the amount was small. By contrast, Pechet and Mac Donald reported that 64% of their "normal" individuals and 80% of the cirrhotic cases exhibited significant amounts of parenchymal iron. In their cases of "alcoholic" cirrhosis large amounts of iron were commonly observed. Dr. Bell emphasized that in his experience with cirrhosis the amount of iron in the liver varied from small to large and that a diagnosis of hemochromatosis on this basis could be made only arbitrarily. Pechet and MacDonald reached the same conclusion, and, as Dr. Bell points out, earlier workers had already been impressed by this continuum. Before considering the significance of this fact we would like to comment briefly on the earlier work from the Boston City Hospital relating hemochromatosis to alcoholism. F. B. Mallory[30] advanced the now well known theory that copper introduced in alcoholic beverages (copper stills) was the cause of pigmentary cirrhosis. This concept has been long since abandoned, but it led to the knowledge that copper is present in excess in the livers of patients with hemochromatosis. Herkel[18] showed that there was commonly an increase of copper in cases of portal cirrhosis without hemochromatosis. Thus it is apparent that the spectrum of copper content, like that of iron, is not well defined nor of a character to permit delineation of the disease. In terms of the essentiality of trace amounts of copper for heme synthesis, it is not surprising to find that it is increased, with iron, in both hemochromatosis and cirrhosis, although a close correlation in the amounts of the two elements has not been shown.

Dr. Bell's study of 932 cases of portal cirrhosis does not provide information as to the proportion that were alcoholic or Laennec in type and those of coarsely nodular, "postnecrotic," nonalcoholic variety. Since the autopsy material during the years represented was largely drawn from the Ancker Hospital in St. Paul and Hennepin County General, as well as the University Hospital, it is likely from our acquaintance with the case material and the proportion contributed by the three hospitals, that from 50-60% of the total were alcoholic-nutritional or primarily fatty cirrhosis. Unfortunately this figure, even if meaningful, scarcely permits any deductions, as about 70% of the 733 cases examined microscopically exhibited no hemosiderin in the liver. Even if but 40-50% of Dr. Bell's cases were alcoholic, it is evident that the incidence of hemosiderosis is considerably lower than the 80% in alcoholic cirrhotics observed at the Boston City Hospital. This difference does suggest that hemosiderosis is more marked in Laennec's than in nonalcoholic, coarsely nodular cirrhosis, and this is borne out by other considerations. This point was also emphasized in the Finches'[11] extensive review* in 1955. They state: "There is a definite association of alcoholism and Laennec's cirrhosis with hemochromatosis . . . The implications in this association are not entirely clear, however. The abnormal diet in the alcoholic conceivably may be a factor in increasing iron absorption; likewise the possibility exists that liver disease may result in greater iron retention through decreased iron excretion in the bile." In the latter connection the Finches were apparently unaware of Eppinger's interesting studies[10] of the bilirubin-iron ratio in the duodenal contents of normal individuals and patients with a variety of diseases, including various types of anemia, polycythemia, hepatitis, ordinary cirrhosis, and hemochromatosis. In the latter the amount of iron was quite small and the bilirubin iron ratio high. Since this related to duodenal contents rather than to pure bile, the possibility cannot be excluded that excessive iron absorption in the duodenum had already occurred. However, this seems less likely in view of the fact that the samples represented two to four hours of continuous suction.

The work of the Gillmans[13] emphasized nutritional factors; their observations revealed that in the South African Bantu, a diet often productive of pellagra but unusually rich in iron is associated with marked hepatic hemosiderosis and a relatively high incidence of pigmentary cirrhosis. Kinney and co-workers[14] have shown that the same type of diet is low in phosphate, thus promoting iron absorption and hepatic hemosiderosis in rats. This has recently been shown to be reversible.[24] Mukherjee and Sarker[32] reported similar reversibility in human protein malnutrition. The excess iron in the Bantu diet has been ascribed to the Kaffir beer which they drink, to the corn of their "mealie-pap," and to the iron pots in which it is cooked. MacDonald[28] has re-emphasized the relatively high iron content of wines commonly drunk in Boston, ascribing considerable significance to this fact in relation to the high incidence of alcoholism (85%) in cases of hemochromatosis studied at the Boston City Hospital.[29]

Alcoholism might also promote increased iron absorption by virtue of pancreatic injury and interference with external secretion of the pancreas. Although there is as yet insufficient evidence of this relationship, there is enough to suggest that it might be a significant factor. One of us, (M.J.M.), in a work which will be published separately, has obtained decisive evidence that diminished external secretion of the pancreas promotes iron absorption. Furthermore, this study has clearly revealed that a protein constituent of pancreatin, as yet unidentified, complexes with added Fe^{59}, after which it is nondialyzable. Biggs and Davis[3] have recently reported signficant reduction in absorption of Fe^{59} in cases of idiopathic hemochromatosis when a potent pancreatic extract was given. The presence or degree of alcoholism was not stated, but they believe this observation supports the hypothesis of a primary pancreatic defect. Yet in cases of advanced chronic pancreatitis or pancreatic lithiasis, there has been no definite association with any marked hemosiderosis of the liver, and it seems unlikely that reduced pancreatic secretion is more than a contributory factor at most.

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*This related to 707 cases published since the 395 discussed by Sheldon.

Genetic Factors

With these various factors in mind the question previously raised as to whether hemochromatosis is simply an acquired disease may be considered in greater depth. In support of this idea Pechet and MacDonald point to the high incidence of stainable iron in various tissues from 125 unselected autopsies at the Boston City Hospital and state that previous studies ascribing hemochromatosis to genetic factors failed to include data on the amounts of iron in the tissues of the corresponding populations. This would refer to papers such as that of Brick,[5] in which liver biopsies were carried out in six asymptomatic siblings, whose father died at age 50 with classical hemochromatosis (necropsy). The father's brother, uncle of the six siblings studied, had also died of "bronze diabetes" at 54, a clinical diagnosis of hemochromatosis having been well established. The liver biopsies from the six siblings revealed iron deposition in all — in one sufficient to warrant the diagnosis of hemochromatosis, while in two others there were already definite histologic changes indicating early cirrhosis. Brick believed that these findings were in accord with complete penetrance of a dominant gene, whereas an incomplete penetrance was suggested by the Finches. It appears unlikely that such marked deposition of iron in the livers of children whose father and uncle died of hemochromatosis is related simply to regional factors. As Sheldon already emphasized, quite a number of familial instances of hemochromatosis, without history of alcoholism, had been recorded prior to 1935, and many more were noted in the 707 cases reported since then and up to the Finches' review in 1955. The Finches also provide extensive data on the high incidence of elevated serum iron values among relatives of propositi with well established hemochromatosis.

Others[21] have recently added strong evidence of the genetic basis of classical or primary hemochromatosis. Heilmeyer[15] credits Kalk with having first observed excessive hepatic iron in early youth in latent familial cases. He cites a doctoral thesis of Rosenhainer to the effect that 120 of a total of 1500 cases of hemochromatosis were clearly familial (see below). Lange[27] has contributed a valuable detailed statement on the genetics of hemochromatosis in which special emphasis is given to what Schapira and Dreyfus[37] called the "géne hypersidérémique."

At the same time that the above-mentioned paper of Pechet and Mac Donald appeared, their question as to regional or population factors in respect to iron intake was answered by an extensive study of several families, reported by Scheuer, Williams and Muir,[38] which included 16 cases of hemochromatosis among 46 close relatives, mainly siblings or children. In addition, comparable observations were made in one patient with alcoholic Laennec's cirrhosis and hemosiderosis, who had three close relatives. In 74% of the 46 relatives of the cases of hemochromatosis, there was excessive iron in the liver; but this was not observed in any of the relatives in the patient with alcoholic cirrhosis. Two hundred and twenty-nine biopsies from 161 patients with hepatic disease, from 39 with nonhepatic disease, and from 29 accidental or suicidal death victims were examined for iron. The percentages of these three groups exhibiting stainable iron was 29, 36 and 28, respectively. This study thus offers the strongest support, if not indeed incontrovertible proof, of the genetic nature of classical hemochromatosis.

Another highly important recent observation in this connection was reported by Brunner and Frick.[6] They found that after oral Fe^{59}, the surface counting over the liver was significantly greater in primary hemochromatosis, in both propositi and relatives, than in cases of secondary hemochromatosis. A striking example was the 13-year-old son in a classical case of (nonalcoholic) hemochromatosis. In this boy the serum iron was over 200 $\mu g\%$, and on giving Fe^{59} orally a striking elevation of surface count over the liver was observed. The boy, however, had no symptoms, skin pigmentation, or hepatic enlargement.

There are many features of the cases studied at the Boston City Hospital which indicate that they belong in very large proportion to the alcoholic-nutritional-pancreatic, acquired category of hemochromatosis. Of the 57 cases diagnosed as hemochromatosis by MacDonald and Mallory[29] on the basis of "tissue damage," 22 of 26 with adequate histories were alcoholics; one of the remaining four gave an unreliable history at least in view of a fatty liver at autopsy; and two of these four had obvious malnutrition. Of 31 of the 57 without clinical records, about one half had significantly fatty livers and cirrhosis. Fatty liver is conspicuously lacking in cases of primary, nonalcoholic hemochromatosis which develops despite a normal state of nutrition. The large liver of primary, nonalcoholic hemochromatosis is relatively nonfatty, whereas in the earlier stages of Laennec's cirrhosis fatty liver is usual. In the former the liver usually remains large up to the time of death; in the latter it commonly undergoes atrophy.[39] Furthermore, the incidence of jaundice and ascites in the 57 cases was remarkably high: 39% for the former, 53% for the latter. In general, primary hemochromatosis exhibits these manifestations in relatively minor degree; in fact, any marked degree of jaundice militates against the diagnosis of primary or hereditary hemochromatosis. Sheldon found mention of jaundice in only seven cases, and then but slight in degree. Ascites was recorded in 67, or 22%, but commonly only as a late or terminal event.

The incidence of chronic alcoholism of 85% of the cases of MacDonald and Mallory is far in excess of the 29% which the Finches found in "all adequately detailed case reports" among 80 of their own and 707 histologically proven cases from the literature. Of the above mentioned 1500 cases of Rosenhainer, 25% were classified as alcoholic, which agrees with Sheldon's statistics if the cases are included in which no history of alcoholism was mentioned in the report. Of those in which it was mentioned, 70% gave a positive history. Sheldon, however, lays much more emphasis on the significant proportion in which it was stated that there was no alcoholic history. These numbered 25% of the total, and on this basis he concluded that alcohol was not a primary factor. Sheldon, however, made no attempt to distinguish between primary and secondary forms of hemochromatosis.

Hemofuscin

The study of Scheuer and his co-workers[38] stimulates renewed thought about v. Recklinghausen's noniron pigment "hemofuscin." Although Sheldon evaluated the scant available knowledge of this pigment up to 1935, its nature and significance are still not understood, and until quite recently discussion of it has been largely neglected. Dubin[9] observed that it behaves in identical fashion histochemically with the "wear and tear" pigment "lipofuscin." Since Dubin found no evidence to support v. Recklinghausen's idea that the pigment is derived from hemoglobin or blood, he suggested that the term "lipofuscin" supplant "hemofuscin." Scheuer,[38] with the electron microscope, noted that in many of the above mentioned biopsies of the relatives of hemochromatosis patients, lipofuscin was in prominent association with ferritin. Because of this it was suggested that it may form the basis of hemosiderin granules, and that therefore ferritin may stimulate lipofuscin formation in some cases, perhaps in excess of the requirement to form hemosiderin granules. This would be in accord too with the fact that lipofuscin is not specific for hemochromatosis but is seen in Bantu nutritional hemosiderosis and in other conditions. It is also possible that concomitant injury, unrelated to ferritin, is responsible for the excessive lipofuscin. The latter has also been noted to accompany excessive iron at an early latent stage of the hereditary disease. Thus Johnson and Frey[21] observed lipofuscin and increased iron in liver biopsies of a son, a nephew and a grandnephew, and a niece of such a case.

An individual with latent hemochromatosis as an inborn error, who becomes a chronic alcoholic, will probably develop bronze diabetes and pigmentary cirrhosis with even greater rapidity. There is little doubt that such combinations of genetic and acquired hemochromatosis have occurred. Proof of such a relationship in a chronic alcoholic would require a study like that of Scheuer's (see above), including positive observations in younger, nonalcoholic members of the family, together with negative control observations on normal subjects in the vicinity.

It must be emphasized that the classical triad of pigmentary cirrhosis, melanoderma, and diabetes mellitus is not in itself pathognomonic of hereditary hemochromatosis, as Dr. Bell's data clearly show. In the absence of alcoholism, dietary deficiency or chronic anemia, when accompanied by a high serum iron, (> 175 μg%), the triad offers indubitable evidence of primary or hereditary hemochromatosis, and in such instances it may be expected that family members will also exhibit evidence of the disease, at least in latent form.

Serum Iron

R. B. Howard[20] observed a number of years ago that the serum iron in 17 of 18 cases of Laennec's cirrhosis is in the low normal range or slightly reduced. This work is in accord with the observation of Block[4] that the serum iron is usually low in patients with simple hemosiderosis in contradistinction to the high levels of hemochromatosis. In one of Howard's 18 patients it was markedly increased, 316 μg%, but in one month's time, with successful treatment, it declined to 36 μg%. Howard concluded that an increase in serum iron in cases of Laennec's cirrhosis pointed to an actively deteriorating status; when the condition was static or improving, the value was in the low normal range. Of the 15 in the latter category it may be assumed, on the basis of Dr. Bell's statistics, that about one third, or five cases, had excessive iron in the liver. From these and other observations it is clear that there may be highly significant increases of hepatic iron without elevation of the serum iron. It seems likely that normal serum iron values would have been observed in at least a fair proportion of the alcoholics with hemochromatosis in MacDonald and Mallory's series; but this study did not include data on the serum iron.

The diagnosis of primary hemochromatosis cannot be entertained unless the serum iron is significantly elevated. In the Finches' personal series 31 of 32 cases had values above 175 μg%. In the 92 cases they collected from the literature in which serum iron determinations were available, 82 had values above 150 μg%; 10 were below. The great majority of the values exceeded 175 μg%. It would be of interest to know whether alcoholism was unduly prevalent in the 11 cases with low values; and in the future it would be highly desirable to study the serum iron of family members of alcoholics presenting features of hemochromatosis, especially if the propositi are noted to have normal values.

Sex Incidence

Sheldon stated that the male to female incidence was at least 20:1, but the Finch survey of a much larger case material indicated about 10:1. In any event a sufficient number of females are represented to exclude the possibility of a sex-linked genetic abnormality. Although Sheldon referred to endocrine differences, he did not mention the most obvious and likely explanation of the differing sex incidence: the loss of iron with menstruation, pregnancy and lactation. The Finch review considers these factors in some detail, pointing out that normal menstruation alone can account for 10-15 gm. of iron, which they think ought to delay the onset at least ten years in females as compared with males. In their series, however, the average age of onset of symptoms in females was 52 as compared with 48 years in males. They grant that this is "surprisingly narrow," but they think that the history of absent or scanty menstrual flow in 50% of the women developing the disease may explain the discrepancy. Nevertheless, certain cases are encountered which are difficult to understand, and we wish very briefly to record one which has been of considerable interest.

Case Reports

Case 1

A 46-year-old white housewife had symptoms of weakness and fatigue of one year's duration. There had been no significant illnesses in the past and no pregnancies. Menstruation was normal at 28-day intervals with a four-day flow. There was no history of alcoholism. The patient was menstruating at the time of the first examination here. Her home physician, Dr. J. Gordon Hyslop of Perth, Australia, had noted a grayish pigmentation of the skin and a serum iron value of 276 μg with 94% saturation. Because of this the diagnosis of hemochromatosis was made. On examination mild pigmentation of the skin was noted, especially over the legs. The liver was barely palpable. There were no other significant abnormalities. The hemoglobin was 15.7 gm., hematocrit 46%. Serum iron ranged from 245-286 μg%. Many other studies including glucose tolerance, serum bilirubin, cephalin flocculation, and bromsulphthalein tests were normal. A skin biopsy revealed iron around the lamina propria of sweat glands and near the blood vessels. A liver biopsy at peritoneoscopy revealed mild portal fibrosis and extensive hemosiderosis of liver cells, characteristic of hemochromatosis.

Serial phlebotomy* was commenced in January 1960, about two years after onset of above symptoms. In January 1961, after removal of 32 pints of blood, the patient felt greatly improved, but the serum iron was still 241 μg%. The hemoglobin was 14.3 gm. In March 1961, after a total withdrawal of 37 pints, the hemoglobin was 12.7, but the serum iron had fallen to 57 μg%. Without further bleeding it rose to 185 μg%, but by August 1, after 41 pints had been removed, the serum iron was 43μg%. At this time she felt entirely well. We have had no further opportunity to study her. It is believed, however, that she will require continued phlebotomy at appropriate intervals, or the use of the new iron chelator, desoxyferrioxamine.[17,42]

This case is an excellent example of idiopathic hemochromatosis in a menstruating female. Although the liver was not greatly enlarged, it already contained large amounts of iron and was mildly cirrhotic by the time the patient was 46. No evidence of diabetes had yet appeared. It would be of great interest to know the serum iron values of her siblings; but this information is not available.

Milliken and Brown,[31] in 1963, reported a case of this type, stated to be the fourth in the literature. At age 40 their patient had had nine pregnancies. In such patients one can only assume that the iron balance has been positive for many years despite relatively normal menstruation.

Portacaval Shunting

Dr. Bell's study revealed that the hepatocellular changes of cirrhosis are not in themselves responsible for hemochromatosis, as the same changes are noted in the majority of cases unassociated with increased iron. MacDonald[28] believes, however, that the portal cirrhosis is the cause of the accumulation. Neither these nor other studies inform us, however, as to the degree of portal obstruction and of portal collateral circulation, and also the extent to which these are correlated with hepatic iron content. This question assumes considerable significance in view of recent observations that portacaval shunts in man and experimental animals are followed by iron deposition in the liver of the same magnitude as in typical hemochromatosis. The first example of this kind to come to the author's attention is highly instructive. This case has already been referred to briefly by F. W. Hoffbauer[19] in a paper on primary biliary cirrhosis.

Case Report

Case 2

A 61-year-old housewife had had a two-week attack of jaundice at age 30, and at age 48 another attack, with pruritus and dark urine. At age 50 she underwent common bile duct exploration and T-tube drainage with relief of itching and disappearance of jaundice; but her symptoms recurred several months later after the tube was removed. At age 54 hepatosplenomegaly, jaundice and excoriations were present. At age 60 an end-to-side portacaval anastomosis was performed because of recurrently bleeding esophageal varices (2-1-56.) The liver biopsy

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*Dr. A. Sigrid Gilbertsen kindly followed this patient in the Hematology Clinic, supervising phlebotomies over the period referred to.

(Fig. 1a) demonstrated "parenchyma greatly altered in architecture, liver substance reduced to small nodules of hepatic cells within dense fibrous tissue. The lobules are distorted and there are collections of lymphocytes in the fibrous tissue. The liver cells frequently show bile pigment and there are some bile thrombi in the capillaries. The remaining liver cells show some degeneration at the margins of the nodules. Conclusion: Portal cirrhosis." There was no evidence of hemosiderosis.

After the operation there was a greater degree of jaundice and pruritus until the patient's demise on January 2, 1957. The autopsy report* stated: "The liver is greenish brown, coarsely nodular, with individual nodules up to 1.5 cm. Segments of pancreas and adjacent lymph nodes are brown in color. The gastric mucosa is distinctly brown. Microscopically the liver illustration shows the pattern of postnecrotic cirrhosis with intense iron pigmentation of the hepatic cells. Fig. 1b Pigment in the scarred areas is negligible. The pancreas shows heavy parenchymal accumulations of iron. A peripancreatic node is pigmented with iron. The spleen shows hyperplasia and fibrosis but there is no iron except in focal areas of less disturbed structure. The stomach shows hemosiderosis.

Comments

This is an unusual hemochromatosis. It is remarkable that the pigmentation has developed since the operation early in 1956. Our liver biopsy at that time is free of pigment.

It was learned subsequently that the patient had received oral iron during much of the 11-month interval between operation and time of death, but she had also received it intermittently prior to operation. One may reasonably assume that if portacaval shunting induces hepatic hemosiderosis (see below), this would be exaggerated in an individual with anemia, receiving oral iron. The extent to which this has been a factor in the cases thus far reported cannot be determined. Case 2 had an iatrogenic form of hemosiderosis in the sense that despite long-standing cirrhosis prior to the shunt, there was no accumulation of iron in the liver, but that this appeared in massive extent after the shunt.

Similar observations by others[36,40] and the experimental production of hepatic hemosiderosis by means of portacaval shunt[7] raise the question as to whether a portosystemic shunt, developing as a result of cirrhosis, may constitute an important factor in causing iron deposition in the liver in patients with cirrhosis. In apparent opposition to this is the general experience that in nonalcoholic, coarsely nodular ("postnecrotic" or "posthepatitic") cirrhosis any simulation of hemochromatosis on the basis of hepatic iron content has been unusual as compared with alcoholic, Laennec's cirrhosis. Portacollateral shunting might have to be of sufficiently great extent (as in the above case or in some cases of alcoholic cirrhosis) or it might serve as an adjunct in the presence of chronic alcoholism, nutritional deficiency, and diminished external secretion of the pancreas.

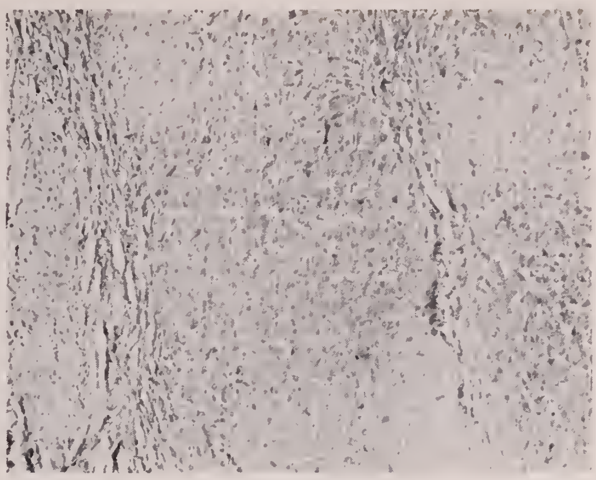

Figure 1a

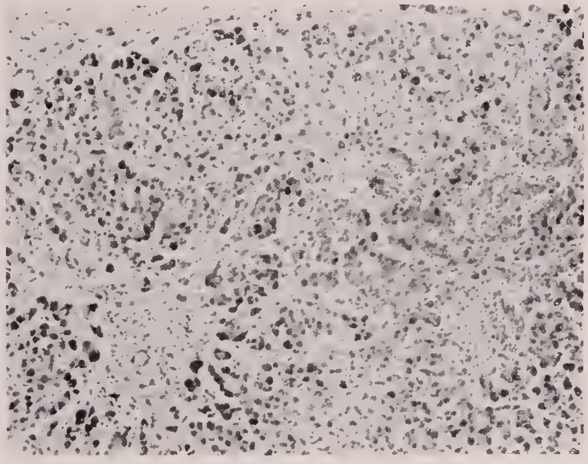

Figure 1b

Fig. 1 — Liver sections stained for iron with Prussian blue reaction x 125. (a) Biopsy at time of portacaval shunt, essentially negative for iron. (b) Obtained at necropsy; the prominent dark areas were intensely blue, positive for iron.

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*By Dr. Robert Hebbel.

It will be of great interest to determine in the future the extent to which portal-systemic blood flow is implicated in the production of secondary hemochromatosis in the chronic alcoholic. It is evident from the above case alone that the iron deposition after the portacaval shunt was not limited to the liver but was also marked in the pancreas, lymph nodes and stomach. This might suggest that the shunt induced excessive iron absorption; but the time interval (11 months) appears to be much too short in relation to the massive hemosiderosis. This was also the opinion of Doberneck et al.[7] with respect to Eck fistula in dogs, and 17 cases of post-shunt hemochromatosis which were collected from the literature. These workers, in addition, found no increase of Fe^{59} absorption after production of Eck fistula in dogs. They ascribe this form of hemochromatosis, both in dogs and humans, to the reduction in hemoglobin formation, as previously shown by Whipple and co-workers,[41] the unused iron thus provided being stored in the liver and other tissues.

The possibility that portacaval shunting induces an increase of retentiveness of iron by the liver cannot be excluded; indeed, such an increase may be induced by various types of liver injury[25] and might well promote a vicious cycle in any of the forms of hemochromatosis, especially if one believes that iron in great excess may be injurious. This poses the final question:

Toxicity of Excess Iron

Does the greatly excessive iron in itself produce damage resulting in hepatic and pancreatic fibrosis? MacDonald has recently answered this question categorically, as follows: "Since iron is not the cause of hemochromatosis but merely colors our livers and our thinking, merely attracts and diverts us, we can get on with a more fundamental and important question. What causes cirrhosis with all its consequences and complications?" Dr. Bell approached this question more cautiously: "It cannot be maintained that the accumulation of hemosiderin in an organ is harmless, since in a few instances massive hemosiderosis of the myocardium has caused cardiac failure. It also appears that subjects with massive hemosiderosis of the liver are more prone to develop diabetes mellitus. In chronic refractory anemia the increased absorption of iron or failure to utilize it may lead to hemosiderosis which may be associated with cirrhosis. In rare instances typical bronze diabetes develops." The Finches were strongly impressed with the evidence of tissue damage and fibrosis under the latter circumstances. In this connection one of the most instructive cases was reported by Pletcher and co-workers.[34] This was a patient with chronic hereditary nonspherocytic hemolytic anemia who had received an estimated 1300 gm. of iron by mouth, over a 13-year period, and who died of a marked pigmentary cirrhosis with bleeding esophageal varices. The liver weighed 2200 gm. and was chocolate brown and diffusely nodular; the pancreas was also dark brown. The Finches believe that iron in large amount is damaging but that experimental studies have been inadequate in terms of amount or of time: "While idiopathic hemochromatosis takes decades to develop in man, the duration of experiments in animals has been at the most one or two years." Heilmeyer[16] believes that when the quantity of protective protein becomes inadequate for nontoxic storage of iron, the steadily increasing excess becomes damaging. Although excessive intake of iron in otherwise normal individuals does not appear to produce tissue damage, a variety of deforming arthritis associated with extensive hemosiderosis has been described in Manchurian hunters and farmers under the name Kashin-Beck disease.[4] It appears that their wells have an exceptionally high content of iron.

Ethionine[22] and N-2-fluorenylacetamide[23] have been shown to enhance the uptake of both dietary and parenterally administered colloidal iron, with formation of relatively large fractions of insoluble iron. The deposition is preceded by appearance of PAS positive granules[25] in the identical areas in which the iron is deposited.[25] This is associated with diminished acid phosphatase, and it has been suggested that these changes reflect a disturbed protein synthesis.

Insofar as human hemochromatosis is concerned, there is inadequate evidence to ascribe it to acute or chronic liver injury except that related to alcoholism and malnutrition or to portacaval shunting. It would appear unwise to discard the concept that iron is causally related to the cirrhosis of primary hemochromatosis, and it behooves students of this problem to strive to reproduce the same type of iron accumulation experimentally, in terms of amount and duration. Perhaps long-term experiments in primates would be revealing.

Sheldon's concept that idiopathic hemochromatosis is an inborn error is fully upheld at least for the nonalcoholic cases in which an hereditary relationship has been shown, and these are being recorded in increasing number. The genetic enzymatic defect which he presumed to be causative has not been identified. Ayvazian,[1] however, has recently reported a striking lack of xanthine oxidase in the liver of a patient with hemochromatosis. The almost complete absence of uric acid in the blood, and the very small amounts in the urine, initially led to this observation. While Ayvazian[1] recognized the possibility of coincidence, he also pointed to a causal relationship based on the knowledge that xanthine oxidase is essential for the conversion of ferric- to ferrous ferritin. Recognizing that the serum uric acid has been observed to be normal in many cases of hemochromatosis, he suggested that these might be heterozygotic in contrast to his case, which accordingly would represent the homozygotic state. An editorial in the same issue[1] in which Ayvazian's paper appeared points out, however, that this would scarcely account for the increased absorption of iron for which there is so much evidence; in fact, if it be assumed that the intestinal xanthine oxidase-ferritin system normally governs the amount of iron absorbed,[1] a lack of xanthine oxidase might be expected to promote iron deficiency rather than hemosiderosis. The editorial suggests that an abnormal ferritin might better explain the evident hereditary increase of iron absorption. This might accord with Heilmeyer's observation[16] that ferritin is actually increased, the greater the absorption of iron.

Conclusions

There are several types of hemochromatosis:

1. Primary or hereditary
2. Secondary or acquired
    a. Chronic anemic (with or without transfusions, but commonly with oral iron therapy. This includes refractory, hemolytic and primary siderochrestic or sideroblastic types.)
    b. Alcoholic-nutritional. (This relates to Laennec's cirrhosis and embraces the factors of pancreatic insufficiency and spontaneous portal systemic shunting.
    c. Iatrogenic portacaval.

One might question whether the term hemochromatosis ought not to be reserved for the primary classical form, using "hemosiderosis" for all of the forms embraced in the secondary or acquired group. While this would be in accord with the usage of many students of the disease in the past, it must be recognized that cases of the latter category are often indistinguishable from the primary type, either clinically or anatomically. In other words, hemochromatosis as described by v. Recklinghausen can be the end result of quite different pathogenetic factors.

These thoughts about hemochromatosis are submitted with genuine humility in contemplating Dr. Bell's great contributions to our knowledge of this and many other areas of disease.

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15-42. will be in the reprints or may be obtained from the author.

WHAT'S YOUR DIAGNOSIS?

Mr. E. B., a sixty-four year old white male had had a right upper lobectomy for a proven bronchogenic carcinoma. He was in his fourth postoperative day. His general health and physical examination was "normal." There was no evidence of metastasis. The surgical procedure had proceeded uneventfully. In the post-operative period his blood pressure had ranged from 160 to 170/90 and the pulse had remained stable at 90 to 100.

While ambulating he suddenly complained of being weak, became slightly nauseated, but had no particular change in the postoperative chest pain. The nurse put him to bed and noted that he was slightly diaphoretic and had a rapid slightly irregular pulse of 180 to 190. The staff physician was called, examined the patient, and immediately ordered an electrocardiogram.

What is your diagnosis? Turn to page 1201.

IT'S THE LAW

Privileged Communication

Privileged communication does not exist when a specific statute requires a report to be made. Likewise, the principle of medical ethics does not prohibit the disclosure of information about a patient if it is required by law. An attending physician must report directly to the coroner or the medical examiner when death is attributable to accident or unexplained causes, or when there is suspicion of foul play. The reporting requirement does not prevent the physician from rendering the needed medical care.

Stetler and Moritz: Doctor and Patient and the Law. C. V. Mosby Company.

Childhood

The period of human life intermediate between the idiocy of infancy and the folly of youth — two removes from the sin of manhood and three from the remorse of age. — Ambrose Bierce

Coccidioidomycosis

• A • Minnesota • Experience

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HUMAN COCCIDIOIDOMYCOSIS is usually acquired by the inhalation of the infective spores of the fungus Coccidioides immitis. The studies of Charles E. Smith from 1937 to 1939 elucidated the factor of human susceptibility and the relationship to erythema nodosum.[1] These findings were further emphasized during World War II, when large numbers of susceptible service men were trained in the desert areas of the southwestern United States endemic for coccidioidomycosis, and many fell victim to the disease.

Maddy[2] studied the area of endemicity of Coccidioides immitis and found it to be almost synonymous with the Lower Sonoran Life Zone, characterized by high mean January and July temperatures and low annual rainfall. A fine, light soil capable of generating clouds of dust prevails in these areas. Soil cultivation, highway construction, or any similar procedure which creates dust will intensify the infection rate among non-immune residents and travelers within the endemic area.

It has been said that were it not for the continuous influx of a susceptible population into areas endemic for coccidioidomycosis, the disease would become almost exclusively a pediatric problem.[3] As modern means of transportation have made the American population increasingly mobile. each year people move in larger numbers through such areas. The magnitude of this population shift may be seen from the fact that at Walter Reed Army Institute of Research approximately 60 per cent of 337 positive serological tests for coccidioidomycosis were found in persons in hospitals located in nonendemic areas.[4] It has been estimated that the morbidity of primary coccidioidal infection is 25,000 cases per year.[5]

The state of Minnesota has long been known as an endemic area for histoplasmosis, but occurrences of coccidioidomycosis in Minnesotans are regarded as isolated medical curiosities. In the course of evaluating recent cases of mycotic infection seen at the Minneapolis Veterans Administration Hospital, we were surprised to find a nearly equal number of cases of active coccidioidomycosis and histoplasmosis. In 1949 Firestone and Benson[6] reported from this hospital the first case of combined, disseminated tuberculosis and coccidioidomycois. Since then we have observed 20 additional cases of coccidioidomycosis, which are the subject of this report.

Our first objective is to emphasize the fact that primary symptomatic pulmonary coccidioidomycosis as well as chronic residual pulmonary lesions are being seen outside endemic areas. Second, we wish to show that even after a long interval of time the diagnosis can be verified by culture of sputum and surgical specimens. Third, we wish to discuss certain inconsistencies with regard to coccidioidin skin sensitivity. Fourth, we wish to share our experience with serologic cross reactions observed in coccidioidal infections. The clinical problem of differentiating peripheral lung carcinoma from nodular coccidioma will be discussed. We wish to emphasize that a careful history in reference to travel may help to avert the necessity of thoracotomy in these patients. Brief mention will be made of four patients with disseminated or meningeal coccidioidomycosis.

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Clinical Material

Twenty cases of coccidioidomycosis have been studied at the Minneapolis Veterans Administration Hospital since 1948. All but one patient were white male veterans, the exception being an elderly negro male with chronic disseminated disease. A history of travel within an endemic coccidioidal area was obtained in all instances. The spectrum of disease observed included three cases with primary infection, eight with coccidioma, five with pulmonary cavitation, and four with disseminated disease (Table 1). More detailed laboratory observations on these cases are presented in Table 2. The usual presenting complaint was an abnormal chest X ray, taken for minor symptoms. Significant pleural pain was present in 11 cases. Hemoptysis, usually of minor degree, was present in five cases. A toxic erythematous rash was seen during the early stages of two infections. Erythema nodosum was seen in two cases. Erythema multiforme was not observed. Some degree of leukocytosis was frequently present in the peripheral blood, as was a slight eosinophilia. To our surprise, six cases failed to show skin sensitivity to coccidioidin (1:100 dilution). Coccidioidal precipitins or complement-fixing (complement fixation) antibodies were found in the serum of nine patients. All disseminated cases showed a titer above the "critical" level of 1:16, with the exception of one case of chronic coccidioidal meningitis. Positive cultures of coccidioides immitis were obtained in all disseminated cases save one case of meningitis. A histopathologic diagnosis could be made in all instances of disseminated disease at autopsy. Two cases of coccidioidal meningitis were considered acute and one case exhibited a chronic course (11 years). Five illustrative cases of localized disease are presented to point out salient pathologic, serologic and clinical observations.

TABLE I
Spectrum of Coccidioidal Disease in Minnesotans

Clinical Picture	No. of Cases
I. Primary Infection Acute Infiltration → Residual Scar	3
II. Fibrocaseocalcific Coccidioma	8
III. Chronic Residual Coccidioidal Cavitation	5
IV. Disseminated Coccidioidomycosis	1
V. Coccidioidal Meningitis	3
Total	20

Case Reports

Case 1

A 66-year-old white man, known to have had diabetes since 1948, was admitted to the Minneapolis Veterans Administration Hospital on April 29, 1963. Since April 12 he had noted headache, anorexia, chills, night sweats, a dry cough and retrosternal pain. Painful red nodules had developed on his lower legs. The onset of symptoms coincided with his return from an automobile trip to the southwestern United States. His itinerary included Los Angeles and the lower San Joaquin Valley in southern California, and Phoenix, Arizona. He left for Minnesota on April 6. The family dog had also made the trip, and the patient had buried the dog's feces in the desert sands on several occasions.

Physical Findings

A roentgenogram revealed an infiltration in the left mid-lung suggestive of pneumonia or pulmonary infarction (Fig. 1, Page 1192). Upon physical examination the temperature was 101 F. The lungs were clear to percussion and auscultation. Tender, warm, red subcutaneous nodules (erythema nodosum) were seen on both lower legs, predominantly in the pretibial areas.

Laboratory Findings

The hemoglobin was 13.8 gm./100 ml., the leucocyte count 11,500 per mm^3. The blood smear revealed neutrophils 75%; lymphocytes 11%; monocytes 12%, and eosinophils 2%. The erythrocyte sedimentation rate was 72 mm./hr. A urine specimen showed a trace of sugar and albumin. Occasional hyaline and granular casts were present in the urine sediment. A fasting blood sugar was 184 mg./100 ml.

Progress

There was a spiking fever for three days, followed by spontaneous lysis. Skin tests were performed on April 30 and no reaction was observed with purified tuberculoprotein (intermediate strength), histoplasmin 1:100, and coccidioidin 1:100. The coccidioidin skin test was repeated on three occasions with dilutions of 1:100 and 1:10 with negative results. Because of a positive coccidioidin complement fixation test at a titer of 1:2, we wrote to the San Fernando Veterans Administration Hospital for a coccidioidin antigen prepared by Dr. Milton Huppert. On May 17, skin tests with this antigen in a dilution of 1:10 were only weakly positive. On May 29 Dr. C. E. Smith at Berkeley, California found 4+ coccidioidin precipitins at a 1:40 dilution, and the coccidioidin complement fixation test was 4+ at 1:4 dilution.

Sputum cultures on May 3 and May 28 grew out Coccidioides immitis. Planigraphic studies disclosed a fibrotic area in the left mid-lung with pleural thickening. The clinical course was uneventful, and the patient was discharged on June 19. When last seen on July 31, he was asymptomatic and only faint

TABLE 2
Case Summaries

Case #	Patient	W.B.C	E.S.R.	Eosinophilia	Diagnosis made by:	Anatomic Lesion	Skin test*			
							PPDi	Histo	Cocci	Blasto
Primary Infection										
1	W. B. 66 W.♂	11,500	72	2%	Culture: Sputum	Pulmonary Infiltration	0	0	±	—
2	J. N. 22 W.♂	15,050	48	8%	Culture: Sputum	Pulmonary Infiltration	0	2+	1+	—
3	R. W. 60 W.♂	7,800	41	3%	Culture: Sputum	Pulmonary Infiltration	3+	2+	0	2+
Coccidioma										
4	E. A. 67 W.♂	7,850	64	8%	Culture: Surgical Specimen	Coccidioma	2+	0	0	—
5	E. R. 56 W.♂	6,800	8	3%	Skin test Serology	Coccidioma	3+	3+	4+	—
6	J. W. 18 W.♂	15,400	40	0%	Culture: Sputum	Multiple Coccidioma	0	3+	3+	—
7	J. S. 67 W.♂	15,650	60	1%	Culture: Surgical Specimen	Coccidioma	0	0	0	—
8	T. W. 25 W.♂	4,350	2	1%	Skin test, History	Coccidioma	0	0	3+	0
9	N. N. 65 W.♂	4,450	—	6%	Histopathology Surgical Specimen	Coccidioma	1+	1+	1+	—
10	W. K. 32 W.♂	6,900	12	0%	Skin test Serology	Coccidioma	0	2+	3+	—
11	J. E. 40 W.♂	6,750	2	0%	Histopathology Surgical Specimen	Coccidioma	4+	0	2+	—
Cavity										
12	W. W. 39 W.♂	6,550	—	4%	Culture: Surgical Specimen	Cavity	2+	2+	2+	—
13	L. E. 25 W.♂	12,100	13	2%	Culture: Surgical Specimen	Cavity	2+	0	4+	0
14	C. D. 39 W.♂	12,750	9	4%	Skin test History, X ray	Cavity	2+	—	2+	—
15	F. F. 49 W.♂	9,600	30	4%	Culture: Sputum	Cavity	0	3+	1+	—
16	J. L. 30 W.♂	7,200	8	7%	Culture: Surgical Specimen	Cavity	3+	0	0	0
Disseminated										
17	N. S. 81 N.♂	9,300	84	5%	Culture: Sputum Autopsy	Disseminated	0	±	2+	—
Meningitis										
18	D. O. 19 W.♂	12,500	21	—	Serology Autopsy	Meningitis	0	1+	1+	0
19	D. G. 20 W.♂	13,100	30	—	Serology Culture: Arachnoid Autopsy	Meningitis	0	—	0	—
20	L. K. 47 W.♂	10,250	5	4%	Culture: Spinal Fluid, Serology Autopsy	Meningitis	—	—	2+	—

*PPDi = Purified tuberculoprotein intermediate strength. Histo = Histoplasmin 1:100. Cocci = Coccidioidin 1:100. Blasto = Blastomycin 1:100.

residual pigmentation was seen in the areas of the previous erythema nodosum.

This is a classical example of acute coccidioidomycosis ("Valley Fever") with recent exposure in an endemic area and manifestations only on return to Minnesota. The probable incubation period was eight to 28 days. Coccidioides arthrospores are known to be present in some superficial topsoil in significant concentration at the end of the rainy season in April. The fungus may have been inhaled while the patient dug in the loose desert topsoil. The presence of precipitins and complement-fixing antibodies in low titers is characteristic of symptomatic primary infections. In the presence of erythema nodosum, one would expect marked skin sensitivity to coccidioidin, but dermal sensitivity was weak even at the end of six weeks.

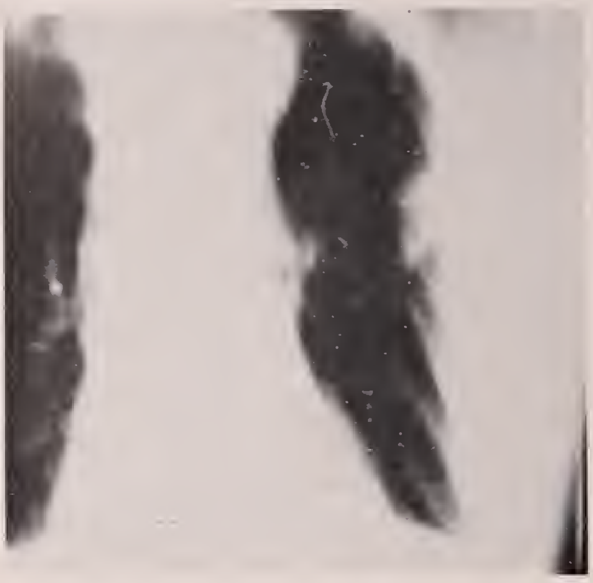

Fig. 1 — (Case 1) Chest planigram showing subpleural fibrotic infiltrate in the left mid-lung field.

Case 2

A 22-year-old man participated in Army maneuvers in the San Joaquin Valley one week prior to his discharge on October 17, 1959. A fellow soldier was reported to have had pneumonia during the maneuvers. A sudden severe left pleuritic chest pain of eight hours duration led to his admission to Minneapolis Veterans Administration Hospital on October 26. On chest X ray a triangular infiltrate was present in the axillary portion of the left upper lobe (Fig. 2).

Physical Findings

The physical findings included marked splinting of the left chest, râles over the left upper lobe, and a temperature of 101.6 F. Blood studies revealed a hemoglobin of 15.8 g./100 ml. and a leucocyte count of 15,050/mm^3. with 2% eosinophiles. The erythrocyte sedimentation rate (Westergren) was 48 mm. in one hour.

Laboratory Findings

The fever disappeared spontaneously on the second day, but chest pain persisted for three weeks, and the eosinophil count rose to 8%. Skin tests were applied on November 1, and the purified tuberculoprotein (intermediate strength) was negative, histoplasmin (1:100) 2+ at 48 hours and coccidioidin (1:100) 1+ at 48 hours. The serum complement fixation test for histoplasmosis (yeast phase antigen) was positive to a titer of 1:8. A serum specimen sent to Dr. C. E. Smith failed to demonstrate precipitins or complement fixation antibodies for coccidioides immitis on November 4, 1959, and again on January 27, 1960. However, coccidioides immitis was demonstrated in the sputum by culture on seven occasions in November 1959. Serial roentgenograms traced the gradual transition to a small residual pulmonary granuloma by April 1961.

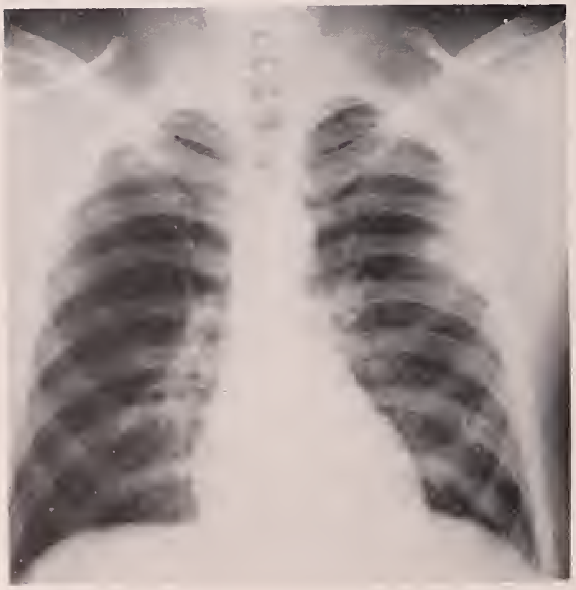

Fig. 2 — (Case 2) Chest roentgenogram showing a soft triangular acute pneumonic infiltrate in the axillary segment of the left upper lobe (extending toward the hilum).

The incubation period of the disease occurred during travel from the endemic area to Minnesota. The infection was focal, hence the serology was not positive to a diagnostic titer and the skin test was only weakly positive. Cross-reactions to histoplasmin suggest previous histoplasma infection. Isolation of coccidioides immitis from the sputum confirmed the diagnosis of coccidioidomycosis.

Campbell[7] has also described low titer serological histoplasmin cross reactions in several patients with coccidioidomycosis whose serum failed to fix complement with coccidioidin. The majority of patients having asymptomatic coccidioidal infections fail to show serum antibodies but often manifest strong skin sensitivity to coccidioidin.

Case 10

A 32-year-old caterpillar tractor operator was admitted to Minneapolis Veterans Administration Hospital on March 26, 1959, because a so-called "coin" lesion was found in the lung on X ray. He had spent November 1958 operating heavy earth-moving equipment near Phoenix, Arizona. At that time he had had a chest cold lasting two days and had coughed up much inhaled dust. In December 1958 he had a sudden severe left precordial chest pain aggravated by respiration. He was treated for two weeks with bed rest for a "heart attack." No chest X ray was taken then, but the electrocardiogram was normal. A chest X ray in April 1958 had also been normal. The film taken on March 26, 1959 revealed a round subpleural lesion 1.5 cm. in diameter in the lower lobe of the left lung (Fig. 3). Planigrams showed no calcification; however, tiny satellite lesions were present suggesting an inflammatory lesion.

Physical Findings

Physical examination revealed a robust white male weighing 208 lbs. The heart and lungs were negative. There were scattered patches of psoriasis on the legs.

Laboratory Findings

The hemogram and urinalysis were normal. An erythrocyte sedimentation rate was 12 mm./hr. Three blood specimens in March were negative for complement fixation antibodies for histoplasmosis, blastomycosis, and coccidioidomycosis.* On April 8 the purified tuberculo-protein (intermediate strength) and histoplasmin (1:100) skin tests were negative in 48 hours. Coccidioidin (1:100) skin test was 3+ positive. Repeat histoplasmin skin test on April 10 was 2+ positive. A serology specimen was sent to Dr. C. E. Smith on April 23, and coccidioidin precipitins were found 4+ at 1:10 dilution and the serum fixed complement with coccidioidin at a 1:4 dilution. By September 14 precipitins were no longer demonstrable. Complement was only slightly fixed at a 1:2 titer after May 26, 1959. Sputum cultures for tubercle bacilli were negative; fungus cultures grew out only Aspergillus and Hormodendrum species. A

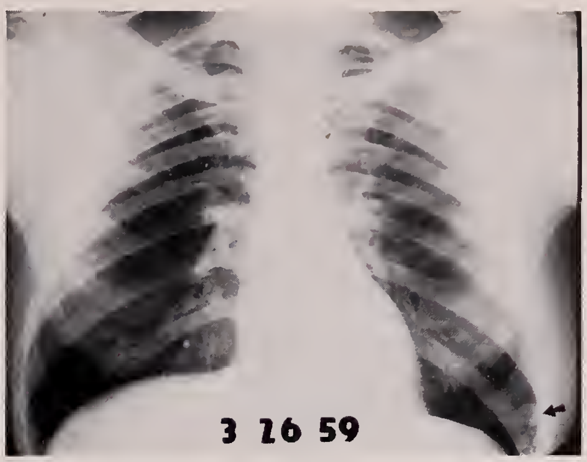

Fig. 3 (Case 10) Chest roentgenogram demonstrating small rounded noncalcified coccidioma near the left costophrenic angle.

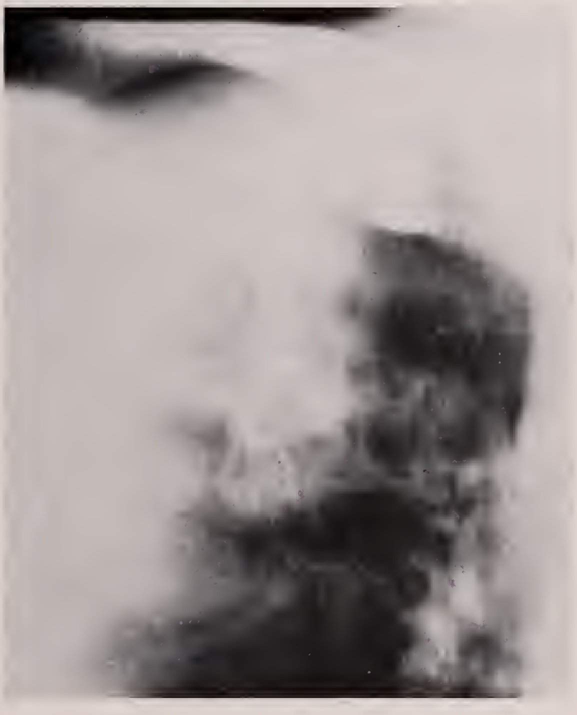

Fig. 4 — (Case 15) Chest planigram illustrating a thick walled chronic cavity in the anterior segment of the right upper lobe.

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*Initial serologic blood specimens were tested by Kennedy Veterans Administration Hospital, Memphis, Tennessee.

thoracic surgeon, fearing cancer, wished to remove this chest lesion, but the patient was discharged on April 24, 1959, and closely watched. The most recent follow-up was on January 14, 1963. Slight calcification was then seen in X rays of the lesion for the first time.

This case portrays a characteristic coccidioidal residual nodular granuloma or "coccidioma." The unexpected discovery on a routine roentgenogram of the chest is typical. Coccidioides immitis is rarely demonstrable in the sputum of such patients because communication with a bronchus is infrequent. Coccidioidin skin tests are usually positive. Coccidioidin serology is often not diagnostic unless the infection is recent. Only rarely is complement fixed beyond a 1:8 titer. According to Birsner[5] 90 per cent of coccidiomas occur more than 5 cm. from the hilus of the lung and the average diameter is 1:3 cm. On serial studies 80 per cent of the lesion undergo some calcification, which may begin as early as three weeks after the initial infection but is often slow in progress.

Unfortunately, the high incidence of malignancy in noncalcified "coin" lesions of the lung forces most of these patients to undergo thoracotomy. This decision may be modified in younger patients with serologic evidence of coccidioidal infection. The proportion of carcinomas among coin lesions of the lung varies with the distance away from an endemic area for coccidioidomycosis.[8] Winn and Evans have found that, among residents of the San Joaquin Valley, less than 1 per cent of "coin" lesions are malignant.[9] Larson and Read[10] studied with acid-fast, Schiff and methenamine-silver stains 75 circumscribed noncalcified pulmonary granulomas at the Minneapolis Veterans Administration Hospital and classified them as follows: Histoplasmona 52, coccidioma 9, tuberculoma 11, and unknown etiology 3.

The diagnosis of coccidioma was made in the present case on the basis of exposure in an endemic area, a positive skin test, and a positive serologic reaction to coccidioidin. The exposure history is important, since the dust blown up while operating a caterpillar tractor may include deeper layers of soil containing focal areas of high arthrospore concentration.

Case 15

A 49-year-old bartender was first seen at this hospital in June 1956 with polyuria, polydipsia and a 40-pound weight loss. A diagnosis of diabetes mellitus was made. In 1943 he had spent four months in an infantry tent camp east of Yuma, Arizona. He recalled no illness nor heavy dust storms at that time. A chest X ray in 1945 had shown a small cavity in the right mid-lung field. In September 1956 a thick-walled cavity 2.5 cm. in diameter was found in planigrams of the anterior segment of the right upper lobe (Fig. 4). For 10 years the patient had had a slight cough productive of a small amount of blood-streaked sputum.

Physical Findings

On admission to Minneapolis Veterans Administration Hospital the patient weighed 146 pounds. Moist râles were heard over the right anterior chest.

Laboratory Findings

Laboratory studies showed a hemoglobin of 14.8 g./100 ml. with a leucocyte count of 9,600/mm^3. The differential count showed 4% eosinophiles. Erythrocyte sedimentation rate was 30 mm./hr. Blood sugar was 224 mg./100 ml. and carbon dioxide combining power 34 meq./liter. The urine contained 3+ albumin, 4+ sugar, occasional hyaline casts and 6-8 white blood cells. Several cultures of urine and gastric aspirations were negative for tubercle bacilli. On September 28, 1956, a sputum culture grew out a smooth, buff saprophytic acid-fast bacillus, which showed a 5+ catalase reaction and was sensitive to streptomycin. Only a few colonies were present, and it was nonpathogenic for guinea pigs. Five sputums and gastric aspirations examined by culture for fungi revealed only Candida, Hormodendrum, and Alternaria species.

Purified tuberculo-protein skin tests (intermediate and second strength) were negative in 48 hours. Coccidioidin (1:100 dilution) showed no reaction after 48 hours. Histoplasmin (1:100 dilution) intradermal test was 3+ in 48 hours. Serum complement fixation tests for histoplasmosis, coccidioidomycosis and blastomycosis were negative in October 1956. Treatment consisted of a 2000 calorie diabetic diet and 25 units N.P.H. insulin.

Progress

On December 17, 1957, complement fixation tests for fungus diseases were again negative. However, the collodion agglutination test with histoplasmin was positive at a 1:32 dilution, and a tentative diagnosis of cavitary pulmonary histoplasmosis was made. During 1957 further sputum cultures for acid-fast bacilli and fungi showed no growth. However, late in 1958 seven sputum cultures grew out Coccidioides immitis. In January 1959, the coccidioidin (1:100 dilution) skin test was 1+ in 24 hours but negative in 48 hours. The collodion agglutination test with the mycelial phase of Histoplasma was still positive at a dilution of 1:8 on January 20, 1959.

In January 1959, the sputum again became negative for pathogenic fungi. Intravenous Amphotericin B therapy was thought to be unnecessary. Serial roentgenograms of the chest showed no change; the sputum remained consistently negative on culture for coccidioides immitis. The last examination was in August 1962.

This case exemplifies the course of a chronic coccidioidal cavity. The disease was present, unsuspected for 16 years, yet viable organisms were then found briefly in the sputum. Although coccidioidal organisms can be cultured from lung lesions after long periods of time, more often they die and calcify in the tissues.[11] It is noteworthy that the coccidioidal skin test was only weakly positive at 24 hours, yet the histoplasmin skin test was strongly positive. The possibility of a nonspecific sensitivity cannot be excluded. The positive collodion agglutination reaction with histoplasmin could also represent a nonspecific cross reaction. Campbell utilized this test only to prove an infection is "mycotic" in origin.[7] It is known that serological cross reactions between Histoplasma capsulatum and coccidioides immitis may occur.

Case 16

A 30-year-old graduate student, was admitted to Minneapolis Veterans Administration Hospital January 25, 1956, because of recurrent hemoptysis. In 1952 the patient had lived nine months in Mexico as a student. He spent 1953 as a postal clerk in Tucson, Arizona, and while there he was exposed to a man with tuberculosis. In 1954 he moved to Minnesota. A chest X ray in November 1955 revealed a cavity in the apex of the left lung.

Physical Findings

Physical examination was normal. A chest X ray verified the cavity in the left subclavicular area. Calcium was demonstrated in the right hilar area. Planigrams showed a thin-walled 2.5 cm. cavity with associated pleural reaction (Fig. 5).

Laboratory Findings

The hemoglobin was 15.9 gm./100 ml. The leucocyte count was 7,200/mm^3 with 7% eosinophiles. Erythrocyte sedimentation rate was 8 mm./hr. Three gastric aspirations, a bronchial washing and eight sputum specimens were negative for acid-fast bacilli on culture. Sputum obtained on February 1 and February 23, 1956, grew out Coccidioides immitis.

On January 26, 1956, a purified tuberculo-protein (first strength) skin test showed a 3+ reaction in 48 hours. Histoplasmin (1:100) and coccidioidin (1:100) skin tests were negative. The coccidioidin skin test was repeated on March 11 and was again negative. A blood specimen on March 28 failed to reveal coccidioidal precipitins but fixed complement at a titer of 1:2.

Progress

A thoracotomy was carried out on March 7, 1956. Dense adhesions were found over a cavity in the apical posterior segment of the left upper lobe. A segmental resection was carried out. A subsegmental bronchus was seen to enter a 2 cm. subpleural cavity surrounded by a fibrous wall 6 mm. in thickness. Microscopically, a portion of the wall of the cavity was lined by squamous and bronchial epithelium, but the majority consisted of eosinophilic granular material. Beneath this necrotic material, epithelioid granulomata and multinucleated giant cells were surrounded by granulation tissue heavily infiltrated with lymphocytes. Stained tissue failed to reveal acid-fast bacilli. A periodic acid Schiff stain was negative for mycelium or yeast forms. Culture of the cavity did not reveal tubercle bacilli. Coccidioides immitis was recovered from the cavity by culture. The culture was inoculated into mice, and after seven days spherules with endospores consistent with coccidioides immitis were demonstrated with periodic acid Schiff stains.

The postoperative course was uneventful, and the patient was well on his last visit in July 1962.

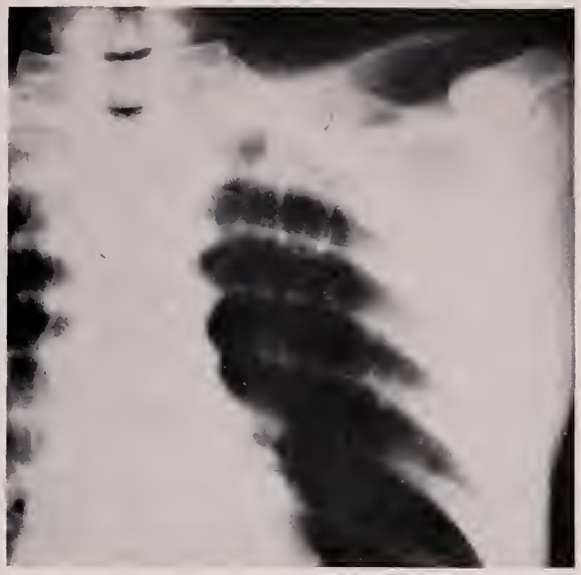

Fig. 5 — (Case 16) Chest planigram revealing a thin walled cavity in the left subclavicular area.

This case is typical of a coccidioidal cavity complicated by hemoptysis. Cotton regarded hemoptysis as a major indication for surgical removal of chronic coccidioidal cavities.[12] In the present case the serologic test was equivocal, with only a 2+ reaction at 1:2 dilution. Smith emphasized that two fifths of patients with coccidioidal pulmonary cavitation have a negative or doubtful coccidioidin complement fixation test.[13] The negative coccidioidin skin test may be ascribed to a waning of skin sensitivity, though Fiese[8] found the number of such cases to be few. A weak commercial antigen or improper administration of the test must also be considered. Chronic pulmonary cavitation appears to follow 2 to 8% of symptomatic primary infections.[13] Superimposed bacterial infection may cause progressive enlargement of coccidioidal cavities.[12] Rupture of a cavity into the pleural space may lead to pleural effusion, empyema, pneumothorax or bronchopleural fistula associated with a recrudescence of the serologic findings.[8]

Discussion

Coccidioidin Skin Sensitivity

Our knowledge concerning dermal sensitivity to coccidioidin stems mainly from Smith's work.[14] During the first week one sixth of patients with primary infections do not react, but by the end of the third week sensitivity is established in patients with primary infections, unless they are undergoing progressive or disseminating disease. In the latter instance, poor dermal sensitivity is often associated with an ominous prognosis. Smith[14] investigated the possibility that strains of the fungus might vary in their antigens. However, strains from widely separated geographic areas and from patients with varied clinical manifestations did not differ. As a precaution multiple strains are used in preparing coccidioidin.

In studying the skin sensitivity of our patients we utilized commercial coccidioidin in a dilution of 1:100 (Tables 2 and 3). Six cases were encountered with positive cultures in which dermal sensitivity could not be demonstrated though tested repeatedly, even utilizing a 1:10 dilution. Two such instances occurred with primary infections.

In two cases of coccidioma operated on to rule out cancer, dermal sensitivity could not be demonstrated, though clinical circumstances suggested that the infection was not in the early stages. In such cases humoral antibodies are also frequently absent. One of our cases of coccidioidal cavitaton (case 5) with positive culture of the surgical specimen failed to react to 1:100 coccidioidin three years after his primary infection. Smith[13] noted only 10 negative skin reactions in 235 cases of coccidioidal cavity. Yet Hyde[15] failed to demonstrate dermal sensitivity in 43% of 77 cases of coccidioidal cavitation, ascribing his poor results to the use of commercial coccidioidin.

In progressive or disseminated coccidioidomycosis, the coccidioidin skin test is frequently negative or weakly reactive. The coccidioidin test was only weakly positive in a case of disseminated disease with erythema nodosum (case 17). Although this symptom is usually considered a good prognostic sign, the patient suffered a fatal dissemination. A negative skin test was also encountered in one of our three examples of acute coccidioidal meningitis (case 19). A positive coccidioidin skin test was demonstrated in one instance of chronic coccidioidal meningitis (case 20).

Serologic Reactions

In a study of 39,500 serum specimens important facts regarding serologic reactions in coccidioidomycosis were established by Smith, Saito and Simmons.[16] In asymptomatic primary coccidioidal infections serologic tests were diagnostic in only 7%, but in symptomatic hospital cases serologic tests were diagnostic in 92%. Positive serologic reactions were present in only 60% of cases of coccidioidal residual cavitation. The majority of tests were negative in patients with other residual lesions. The above authors emphasized that the coccidioidin precipitin test was useful in early diagnosis of many primary coccidioidal infections. Precipitins appeared early, after the coccidiodin skin test converted to positive, and were present by the third week in 91% of their positive cases. During the second month the precipitin titer fell off rapidly, and only 10% of their cases showed positive precipitin tests by the fifth month. Complement fixing antibodies appeared later than precipitins and had special significance in the disseminated infections. Approximately two thirds of patients gave positive complement fixation tests between the second and third month after infection. These antibodies fell off slowly, occasional cases possessing them for several years. Of the primary coccidioidal infections showing positive complement fixation tests, nearly 50% had a titer of only 1:2. Smith felt that the critical serum titer suggesting dissemination was 1:16. Residual coccidioidal cavities were associated with complement fixation titers over 1:16 in less than 3% of cases. In only 1% of solid coccidioidal residual lesions was complement fixed above the critical titer.

Several reference laboratories employing a variety of methods and antigens were used in our cases for determination of coccidioidal antibodies. Smith[17] et al. compared their method (two-hour incubation at 37° C.) with the method utilized at the Walter Reed Institute of Research (18-hour incubation at 4° C.) and showed that the latter gave a five-fold increase in titer. Physicians wishing to use a complement fixation titer as an indication for therapy must know the laboratory and the method in use.

A second consideration in evaluating serologic data in coccidioidomycosis is the stage of the disease. Unfortunately the precipitin test was not done regularly in our cases. We observed positive precipitin tests in only one case of primary infection (case 1) and one case of coccidioma (case 10) (Table 3). Positive complement fixation tests were observed in only one of two primary infections, in three of six coccidiomas, and in one of five cases of coccidioidal cavity. Most large series[13,15] of coccidioidal cavitation have shown 65 to 75% positive complement fixation tests. The low incidence of positive complement fixation tests observed in our patients probably reflects the long delay in diagnosis in several cases (Tables 4 and 5). As shown in three of our coccidiomas, a positive complement fixation test can be a valuable diagnostic aid in patients presenting with a pulmonary "coin" lesion (cases 5, 6, and 10). One patient (case 6), showing multiple nodular densities in the lung, had an ominous complement fixation titer of 1:32, but the titer fell rapidly. Chronic disseminated coccidioidomycosis often gives rise to a persistent complement fixation titer. Chronic coccidioidal meningitis of long duration may be associated with weak positive complement fixation tests (case 20), and the spinal fluid usually fixes complement in low titer.

In evaluating serologic results consideration must be given to cross reactions with other fungal antigens. The pattern in coccidioidal infections has been described by Charlotte Campbell.[7] She stressed that patients with histoplasmosis rarely show cross reactions with coccidioidin in the complement fixation test. When this does occur, it is at a low titer (below 1:20, Walter Reed method) and is associated with high titers with homologous antigen (above 1:160). The coccidioidin complement fixation test is positive at high titers (between 1:40 and 1:1280) in cases of recent dissemination of coccidioidomycosis. Cross reactions with histoplasmin and blastomycin antigens may occur but rarely approach the level for homologous antigen, and are often absent in cases of long duration. Unfortunately, in cases of focal nonprogressive coccidioidal infection, sera may be more reactive with heterologous antigen than with coccidioidin. Even though

TABLE 3
Skin Tests and Serological Tests — Cross Reactions

		Primary Infection		Coccidiomas			Cavity			Disseminated		
Skin Test	Case # →	1	2	5	6	10	15	16	17	18	19	20
P. P. D. int.		0	0	3+	0	0	0	3+	0	0	0	—
Histoplasmin		0	2+	3+	3+	2+	3+	0	±	1+	—	—
Coccidioidin		1+	1+	4+	3+	3+	1+	0	2+	1+	0	2+
Blastomycin		—	—	—	—	—	—	0	—	0	—	—
Serology												
Coccidioidin ppt.		1:40	0	—	0	1:40	—	0	—	1:40	0	0
Coccidioidin C.F.		1:4	0	1:4	1:32	1:4	0	1:2	1:256	1:64	1:64	1:8
Histoplasmosis C.F. (W.Y.P.*)		0	1:8	0	1:8	0	0	0	1:8	0	0	0
Histoplasmosis Collodion Agglutination		—	0	—	0	0	1:32	0	0	0	0	0
Blastomycin C.F. (W.Y.P.)		0	0	0	1:16	0	0	0	1:16	0	0	0

*W.Y.P. = whole yeast phase antigens.

complement fixation antibody to coccidioidin is not found, low titers (1:5 to 1:40) with histoplasmin and/or blastomycin antigens should make one suspect coccidioidomycosis. At Walter Reed Institute of Research 35 cases of coccidioidomycosis were detected by this pattern of reaction with heterologous antigens and later proven by isolation of the organism.[7]

Two of our cases with coccidioidin complement fixation titers of 1:32 or over showed lesser reactions with histoplasmin (whole yeast phase antigen) and blastomycin (Table 3). In patients with disseminated infection these nonspecific cross reactions at low titer should offer little difficulty in diagnosis. Low complement fixation titers with homologous antigen are rarely encountered in disseminated histoplasmosis but are frequent in blastomycosis. One of our cases (case 2) of primary infection showed the pattern described by Campbell,[7] i.e., no reaction with coccidioidin and a low titer cross reaction with histoplasmin whole yeast phase. Also one of our cases of coccidioidal cavity had a positive histoplasmin collodion agglutination test at a titer of 1:32. Campbell[7] found cross reactions so frequently with this test that positive findings were considered merely indicative of a "mycotic" infection.

Chronic Pulmonary Lesions

The coccidioidal pulmonary residual lesions observed after acute pulmonary coccidioidomycosis were linear fibrotic scars, coccidioma, and chronic cavity. The linear fibrotic scar usually represents a healed focus of a primary coccidioidal infection. These lesions have been studied post mortem and may frequently harbor viable fungus for many years.[11] The three cases we studied were proven by sputum culture, but were not studied histopathologically.

Pulmonary coccidioma and coccidioidal cavity are different stages of the necrotic granuloma. Coccidioidal pulmonary residuals are occasionally unstable. Communication with a bronchus may convert the fibrocaseous granuloma into a cavity. Conversely, a cavitary lesion may fill and be converted to a solid coccidioma after obstruction of its bronchus and inspissation of its contents. Despite such occasional fluctuation the coccidioidal residual is rarely a threat as a focus for dissemination. The typical thin-walled cavity has a partially epithelialized wall and few viable Coccidioides immitis. The thick-walled cavity has a heavy fungus infestation near the inner surface of the necrotic lining.

Eight of our patients had fibrocaseocalcific coccidiomas; in seven these were single, and in one case there were five nodular lesions up to 1 cm. in diameter scattered throughout both lung fields (Table 4). The remainder of the cases showed solitary, round, sharply circumscribed lesions, frequently subpleural in location, measuring between 1 and 4 cm. in diameter. These findings are consistent with the coccidiomas described by Birsner.[5] A predilection for the upper lobes of the lung has been recorded by most investigators and was confirmed in six of our eight cases. The majority of these cases were diagnosed within the first year after their primary infection; however, three cases were seen several years after the infections were incurred. Only one (case 5) showed significant amounts of calcium, and the clinical evidence suggested its age was 19 years. Tiny satellite lesions occurred in two cases. In the majority of these patients coccidioidin skin sensitivity was present, but sputum culture and serological reactions were unrewarding. Nevertheless, in one case sputum culture showed coccidioides immitis 10 months after the initial exposure (case 6). Also a second patient showed precipitins and complement fixation antibodies in his serum four months after the onset of symptoms (case 10). The majority of our patients were examined for asymptomatic "coin" lesions found on chest X rays and proven by pathologic study or culture of the surgical specimen. Two patients gave a history of a recent 'heart attack' while in Arizona. Close questioning revealed a pleuritic nature to the chest pain.

Among our five cases of chronic pulmonary cavity, two patients had typical thin-walled cavities (Table 5), and one patient had a thick-walled cavity of long duration and a positive sputum culture for coccidioides immitis (case 15). The two remaining cases were nodular fibrocaseous granulomas presenting an X ray appearance of cavitation. The cavities were 2 cm. in average diameter and showed patent bronchi in three cases. All were found in the upper lobes. Satellite lesions were present near the cavity in two specimens, and mycelial forms of coccidioides immitis were present in the cavity wall in one specimen (case 13). Forsee and Perkins[18] found mycelial forms in 50% of 30 cases of pulmonary coccidioidal cavitation. This raises the theoretical possibility that direct person to person infection might occur; however, no such cases have been reported. Unusual delay in diagnosis was encountered in two of our five cases. In one patient a cavity was complicated by recurrent pneumonia and pleurisy over a seven-year period. Another thick-walled cavity was demonstrated by X ray to have persisted for 16 years, yet spu-

TABLE 4
Coccidioma Residual Lesions

Case #	Patient	Place and time of primary infection	Delay in diagnosis	Size and location of lesion	Satellite lesions	Calcium present	How diagnosed
4	67 W. M.	Arizona last 6 years	?	1.5 cm. nodule L.U.L.	0	0	Culture of Surgical Specimen
5	56 W. M.	California 1943	19 years	2.0 cm. nodule L.L.L.	0	+	Skin test Serology
6	18 W. M.	California October 1958	None	Multiple (5) 1 cm. nodules both lungs	0	0	Culture of Sputum
7	67 W. M.	Tucson, Arizona January 1960	11 months	1.1 cm nodule L.U.L.	+	0	Culture of Surgical Specimen
8	25 W. M.	Texas 1955	3 years	1.5 cm. nodule R.U.L.	0	0	Skin test History
9	65 W. M.	Tucson, Arizona February 1962	6 months	1.8 cm. nodule L.U.L.	0	0	Skin test Histopathology
10	32 W. M.	Phoenix, Arizona November 1958	4 months	1.5 cm. nodule L.L.L.	+	0	Skin test Serology
11	40 W. M.	Williams AFB, Arizona September 1944	6 years	4 cm. mass R.U.L.	0	0	History Histopathology

TABLE 5
Chronic Coccidioidal Cavity

Case #	Patient	Place and time primary infection	Delay in diagnosis	Size and location of lesion	Patent bronchus	Satellite lesions	Mycelial forms	How diagnosed
12	39 W. M.	Tucson, Arizona March 1960	1½ years	1.5 cm. cavity LUL	+	+	0	Culture of Surgical Specimen
13	25 W. M.	Texas, 1949	7 years	2.0 cm. cavity LUL	+	+	+	Culture of Surgical Specimen
14	39 W. M.	Phoenix, Arizona last 8 years	?	2.0 cm. cavity LUL	—	—	—	Skin test X-ray picture
15	49 W. M.	Arizona 1943	16 years	2.5 cm. cavity RUL	—	—	—	Culture of Sputum
16	30 W. M.	Tucson, Arizona 1943	2½ years	2.0 cm. cavity LUL	+	0	0	Culture of Surgical Specimen

tum cultures continued positive for coccidioides immitis.

Mycology

We have enjoyed frequent success in isolating Coccidioides immitis by culture of the sputum or the surgical specimen. Our results are presented in Table 6. We attribute our success to a hospital laboratory staffed by a medical mycologist. Coccidioides immitis was demonstrated on 11 of 16 (69%) coccidioidal cavities or closed pulmonary residuals. Typical arthrospores (mycelial phase) were found microscopically in each of the positive cultures. The identity of the cultures was proven by inoculation intraperitoneally into white Swiss mice, and the mouse tissue was later examined microscopically for spherules with endospores (yeast or tissue phase). Pappagianis[19] compiled from the literature 360 attempts to culture Coccidioides immitis from such residuals with success in 44%. In four of five cavities we recovered Coccidioides immitis by culture of the surgical specimen or sputum. Smith[13] reported positive cultures in 40% of 274 coccidioidal cavities.

TABLE 6
Cultures From Coccidioidal Residual Lesions

	No. of Cases with Positive Culture
Culture of Surgical Specimen (2 coccidioma, 3 cavities)	5
Culture of Sputum (3 primary cases; 1 coccidioma; 2 cavities)	6
Organism not demonstrated by Culture (4 coccidioma, 1 cavity)	5
Total	16

11 of 16 cases proven by positive culture.

Management of Coccidioidal Residual Pulmonary Lesions

Of the 16 cases of coccidioidal pulmonary residuals, seven were subjected to surgery; the remainder were followed medically and serologically. The indications for surgery were pulmonary cavitation with secondary infection or hemoptysis, or undiagnosed "coin" lesion of the lung. Segmental pulmonary resection was the usual surgical procedure.

We observed no cases of bronchopleural fistula, empyema, or recurrent cavitation. The surgical procedures were accomplished without complication. Culture of the surgical specimen revealed Coccidioides immitis in five of the seven cases.

Summary

1. In the past 15 years 20 cases of coccidioidomycosis have been seen at the Minneapolis Veterans Administration Hospital in residents of Minnesota who traveled or worked in an endemic area. They included three cases of acute pulmonary coccidioidomycosis, 13 patients with pulmonary coccidioidal residual lesions, and four instances of disseminated disease.

2. Dermal sensitivity to coccidioidin could be demonstrated in only 14 of 20 cases of coccidioidomycosis with commercial coccidioidin (1:100 dilution).

3. The serum coccidioidin complement fixation test was positive in only nine of 20 cases of coccidioidomycosis. The coccidioidin complement fixation test was negative in four of five examples of chronic coccidioidal cavitation but positive in three of six patients with coccidiomas. Serologic cross reactions with other fungal antigens presented a frequent diagnostic problem but also increased sensitivity in the diagnosis of chronic coccidioidal residuals.

4. Coccidioides immitis was demonstrated by culture in 14 of 20 patients with coccidioidomycosis.

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ANSWER TO WHAT'S YOUR DIAGNOSIS

(From page 1188)

Auricullar fibrillation. This is common in older patients following thoracotomy. Prophylactic digitalization has been used by many to prevent this and the extremes of tachycardia from developing in the postoperative period.

AGAMMAGLOBULINEMIA SYNDROME

(Antibody Deficiency Syndrome)

This condition is characterized by recurrent infections, mainly of the upper respiratory system. The degree of hypoglobulinemia is most readily determined by electrophoretic tracing. There is thought to be a congenital or idiopathic type occurring in early infancy and a second acquired type seen in adults. This condition should be differentiated from hypogammaglobulinemia which occurs in the course of nephrosis or malnutrition.

Treatment of agammaglobulinemia consists in the administration of antibiotics and repeated intermuscular injections of human gammaglobulin.

Durham-Encyclopedia of Medical Syndromes
Hoeber, Inc., New York

BOAS'S SIGN

In cholecystitis there may be an area of epicritic hyposthesia in the back from about the level of the 11th dorsal to the 1st lumbar on the right side. There may be itching in this area which is not completely relieved by scratching.

Cleanliness

Tolerate no uncleanliness in your body, clothes, or habitation. — Benjamin Franklin

Hypertension in Relationship to

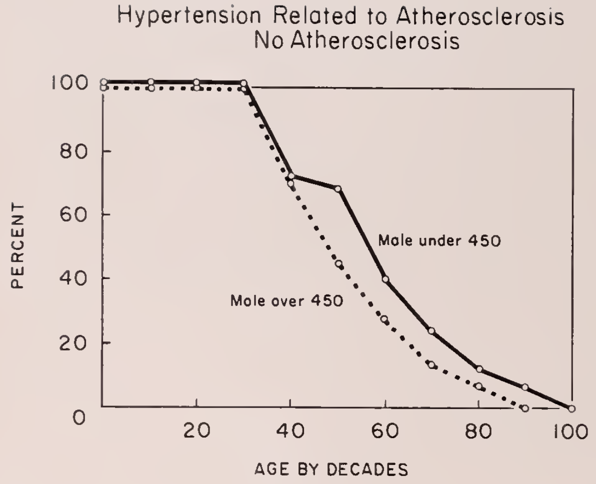

Figure 1

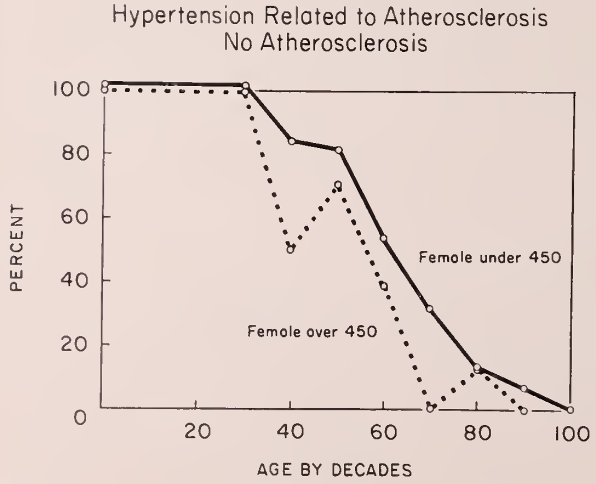

Figure 2

THE LITERATURE reflects general concurrence in the opinion that hypertension accelerates the process of atherosclerosis. Although it would appear that this is true also for the vessels of the central nervous system, very few studies have been carried out on a large enough series of cases to adequately document such a conclusion. This report is based on post-mortem studies on the arterial circle of Willis in 2,388 consecutive autopsies. The degree of cerebral atherosclerosis has been grossly coded according to the method of Baker.[1] We feel that we have been able to demonstrate that on a statistical basis, in a fairly large number of cases, atherosclerosis of the cerebral arteries is also accelerated by hypertension.

Methods and Materials

The material was drawn from routine autopsies performed at the University of Minnesota Hospital and the Minneapolis General Hospital. The former is a teaching hospital and the source of patients is largely rural in origin. They may be private or indigent, the majority probably indigent. There are a lesser number of patients of urban origin, primarily in the private category. In the Minneapolis General Hospital, patient

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Cerebroatherosclerosis

population is urban-indigent in nature. For purposes of determining the presence of hypertension, only the heart weight was considered, a heart weight of 450 grams being taken as evidence of hypertension. There were 1,711 cases in whom the heart weight was under 450 grams and 677 cases in which the heart weight was over 450 grams.

The vessels were coded, as stated above, by the method of Baker.[1] The accuracy of this method has been tested by a number of investigating teams, and there is virtually complete concurrence in the values assigned by separate investigators in recent trials. In the utilization of this system, the vessels of the circle of Willis are carefully inspected grossly; if necessary, a magnifying glass is used to check the areas involved. Section of the vessel is made at the point of involvement to determine the extent of lumen narrowing. The atherosclerotic process is rated from 1+ to 4+ as follows:

- Grade 1+: Opacity involving only a small part of the vessel circumference. No lumen narrowing.
- Grade 2+: (A) A diffuse, thin plaque that does not involve the entire vessel circumference with minimum lumen narrowing.
  - (B) A small, thick plaque that produces less than 25% lumen narrowing.
- Grade 3+: (A) A diffuse, thin plaque involving the entire circumference of the vessel with mild lumen narrowing.
  - (B) A localized, thick plaque producing 25-50% lumen narrowing.
- Grade 4+: (A) A thick plaque involving the entire circumference of the vessel with moderate or marked lumen narrowing (pipestem).
  - (B) A localized, thick plaque resulting in over 50% lumen narrowing.

In order to determine the extent of the total atherosclerotic process, 22 different areas along the circle of Willis are studied and graded according to the degree of the atherosclerotic changes as used in the foregoing system. Each of these 22 areas is graded from 0 to 4+, and the total value for the degree of atherosclerosis is obtained by adding the scores of all the graded areas. Since there are 22 areas to be coded, the most severe change possible would be 22 x 4+ or 88+. None of the cases has shown changes of such a severe degree. In the curves plotted from the data gathered in this study, the term "no atherosclerosis" means a 0 rating throughout. The term "severe atherosclerosis" means a rating of 15 points or more.

Furthermore, in presentation of the data, males have been separated from females, primarily because in a previous report on a series of 3,839 cases, it was shown that severe atherosclerosis was less common in the younger female population than in males of the same age groups.[2] This was patricularly well demonstrated in females of 40 to 60 years, who had from 11% to 19% less atherosclerosis than males of the same age. Beyond the age of 60, there was very little difference between the sexes.

Findings

In Absence of Atherosclerosis

This data has been analyzed from two points of view, viz., absence of atheroscler osis and presence of severe atherosclerosis. Curves have been drawn for males and females showing the absence of atherosclerosis (Figs. 1, 2). It is fairly apparent that atherosclerosis is much less frequent in the nonhypertensive groups of individuals, whether they be male or female. When one compares these two curves (Figs. 1 and 2), it is apparent that atherosclerosis is considerably more frequent in males than in females up to the age of 60 years, regardless of whether hypertension is present or not.

In Presence of Atherosclerosis

Similar findings occur when one studies the prevalence of severe atherosclerosis through the various decades (Figs. 3, 4). One sees again that there is a greater amount of severe atherosclerosis in the hypertensive cases of either sex. In so far as the male and female comparisons are concerned, however, it would seem here that severe atherosclerosis is more frequent in the males up to the age of 60 years and in females beyond that age. Therefore we feel that this shift in frequency of atherosclerosis in the female is directly related to some endocrine factor.

Atherosclerosis vs. Sex

This point is further illustrated by an analysis of the curves for severe atherosclerosis. In Figure 5 the comparison of the data for males and females with heart weights under 450 grams shows that females have less involvement until age 70, after which they surpass males. In Figure 6 a similar comparison is made in patients with a heart weight over 450 grams. Here it would seem that females are less involved for a greater part of the time from age 30 to 60, and that thereafter, their rate quite definitely exceeds that of males.

It was pointed out in the section on methods and materials, in our previous report on 3,839 cases, that the difference between males' and females' prevalence of severe atherosclerosis was negligible after age 60. Yet the data illustrated in Figures 5 and 6 show a definite increase in female prevalence at age 70 in the case of patients with heart weights under 450 grams, and at age

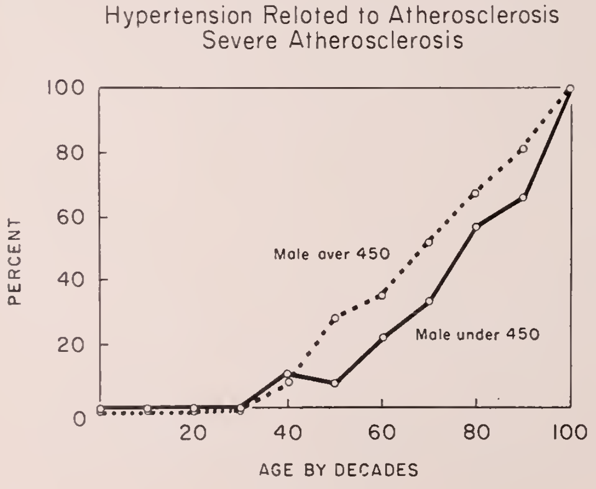

Figure 3

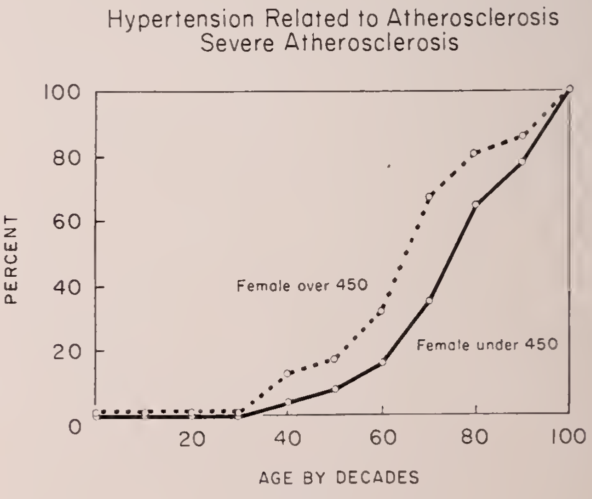

Figure 4

60 in the case of patients with heart weights over 450 grams. This disparity, we feel, may be due, in part at least, to the smaller number of cases on which the comparison was based. Consideration must also be given to the fact that the comparisons made on the larger series did not distinguish between the heart weights over or under 450 grams.

Atherosclerosis vs. Hypertension

A somewhat different analysis than the foregoing showed the effect of hypertension quite strikingly. Patients after the third decade only were considered, since no atherosclerosis occurred before this. The total points of atherosclerosis for all patients with heart weights over 450 grams were divided by the total number of patients in this category. The data from cases with heart weights under 450 grams were treated in the same manner. The average number of points of atherosclerosis for the patients with heart weight over 450 grams was 7.67, whereas for those under 450 grams it was 5.26. An increase of some 46%, therefore, was the result of hypertension.

Discussion

A variety of interesting animal studies suggest an explanation for the effect of hypertension on atherosclerosis. Daly[3] found that hypertensive rats on regular diets showed higher serum and aortic cholesterol than normotensive rats. In parabiotic pairs of rats, in whom one member was made hypertensive, the serum cholesterol was similar in both rats, but the aortic cholesterol was higher in the hypertensive rat. Werthessen,[4] in 1954, showed that in vitro aortas, the perfusate pressure showed a positive relationship to concentration of cholesterol. Stephenson, et al.[5] showed that in dogs with experimental coarctations, the hypertensive segment had the atheroma, after these animals had been made hypercholesteremic. It was the feeling of these workers that basis for atheroma formation was trauma to the vessel wall. Repetitive pulsatile stress caused tissue injury, enhanced by hypertension at points of mechanical fixation. Repair of the injury is attempted in the presence of high cholesterol, resulting in the lesion. Physical factors, they believe, act by interference with lipid transport across arterial walls, as well as producing trauma to the wall. Sako[6] also performed dog experiments. In cases with surgical coarctation in artificially hypercholesteremic dogs, he found that hypertension in the coarctation area accelerated atherosclerosis. He noted that each dog serves as its own control, since the disturbed dynamics were only in the surgically altered section of the vasculature. His animals were followed for periods of many months and it was found that disparity of atheromatosis between the altered segments and the rest of the vasculature persisted for 18 to 24 months.

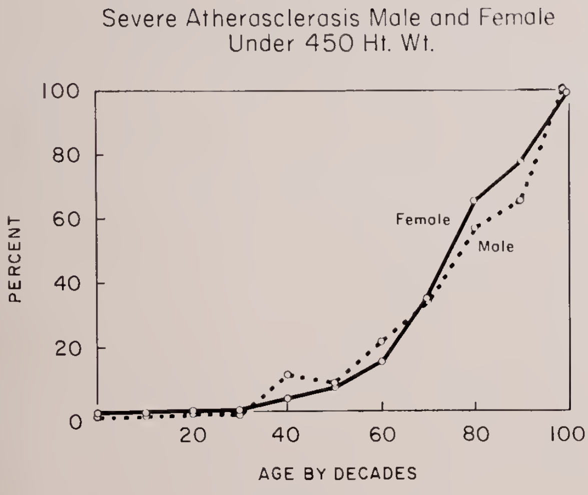

Figure 5

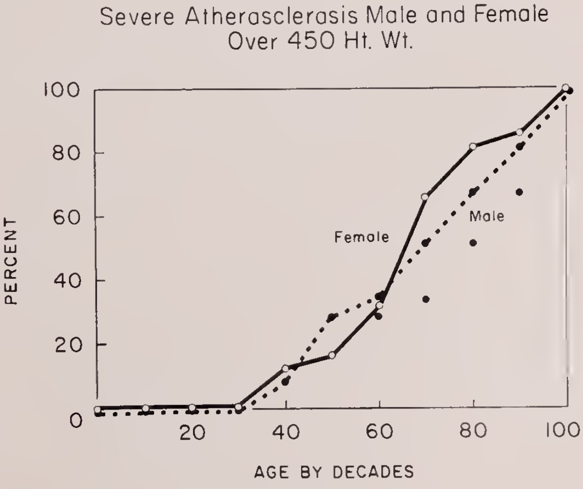

Figure 6

Laplace's Law

Theoretical explanations are offered by a number of authors. Willis,[7] in 1954, advanced Laplace's Law ($T = P \times R$, when T is the total tangential tension in dynes per square centimeter and R is the radius in centimeters. One millimeter of Hg = 1330 dynes/cm^2). Important components of this law are the blood pressure in the artery and the surrounding tissue pressure, as well as the radius and curvature of the artery. Although he acknowledges that hypertension is frequently associated with atherosclerosis, he states that it is only one of several factors. He cites natural occurrence of local hypertension, as in pulmonary hypertension, in coarctation, and also in epicardial branches of the coronaries, as being a factor in the local production of atherosclerosis. As one inspects the Laplace equation, it is apparent that the greater the radius, the greater the tension. We have previously commented on the fact that atherosclerosis is generally more prevalent in cerebral vessels of greater diameter. Hass[8] remarked on the fact that in man it is generally conceded that the level of blood pressure, in excess of vessel design to withstand it, increases the probability of atheromatous accumulation, and he offered as examples the pulmonary artery atheromatous changes in mitral stenosis and the presence of atheroma in veins subjected to excessive pressure. Lansing[9] also utilized the pulmonary artery in his discussion on atherosclerosis and the nature of the arterial wall. He felt that the receptivity of the arterial wall to cholesterol is the major factor in atheromatosis. Ordinarily, the pulmonary artery is free of this difficulty, but, in pulmonary hypertension, one does get into trouble, presumably because the excess pressure causes a breakdown in the elastic lamellae, which necessarily precedes atheromatosis. He had further interesting comments on phylogeny, stating that arterial degeneration is seen in all animals as well as in birds, but that modern reptiles do not have the disease. He noted that reptiles have double aortas and that their blood pressure is only about one half that of birds and mammals. Duguid,[10] in 1926, discussed the role of hypertension in atherosclerosis. He suggested that factors which increase the range of pulse movement increase the liability of atheromatous changes, and of these factors the most important are hypertension and the strain caused by the focal fixation of the aorta by its branches. Analogous situations are certainly present in the cerebral vasculature. Stamler,[11] in a paper on the interrelationships of the two diseases, hypertension and atherosclerosis, stated that the two are separate disease processes produced in animal experiments by different methods, e.g., the Goldblatt preparation for hypertension and hypercholesteremic diets for atherosclerosis. On an epidemiological basis, he also differentiates between the diseases by noting that the prevalence rate of atherosclerosis is different between men and women, but that this is not the case in hypertension. From the clinicopathological viewpoint, he brings out that coronary artery disease and cerebrovascular accidents occur in normotensive old people, indicating the independent disease process known as atherosclerosis. On the other hand, one has cerebrovascular accidents as the basis of hemorrhage in hypertensive people in whom no atherosclerosis is seen. The diseases, however, do interrelate. Renal artery atherosclerosis, for example, causes hypertension in animal experiments. Furthermore, atherosclerosis is shown to be accentuated by hypertension. In humans, hypertension also causes greater incidence of coronary disease. Moga et al.[12] reported on the increase of cholesterol, total lipid and beta lipo-protein levels in hypertensive individuals. They also commented that the increase in men appeared in the 50-60 year decade and, in women, in the 40-50 year decade. They suggested a correlation with the menopause in the latter, stating that women, before menopause, have a relative immunity to atherosclerosis. They felt that the relationship between the two diseases, hypertension and atherosclerosis, brings data in support of the neurometabolic theory of the etiopathogeny of atherosclerosis, a theory put forth by the Soviet school (Anichkov, Maskinov).

Human pathological studies are of considerable interest. Robertson,[13] in a series of 738 autopsies in Jamaica, studied the cerebral vasculature in 284 cases, using an atherosclerotic index (Moosy Technique). In these 284 cases, he found 14 with hemorrhage and 12 with softening. All of the hemorrhage cases were hypertensive. It was also found that generally the hypertensives had a more severe degree of atherosclerosis, but that not all of the severe atherosclerosis cases had softening. It was of further interest that not all softenings in the hypertensives had severe atherosclerosis. Robertson stressed the wide individual variations and, therefore, the need for a larger series, a recommendation with which we can heartily concur. He did feel that hypertension accentuated atherosclerosis, especially after the menopause in women. Young et al.[14] in 95 of 143 cases, was able to correlate antemortem blood pressure with atherosclerosis. His numbers were small; but statistically he has proven that systolic and diastolic pressure are significantly correlated with the degree of coronary and cerebral atherosclerosis, the strength of the correlation being greater for the cerebral than for the coronary vessels. The strength of the correlation was less for both cerebral and coronary vessels in subjects in the 79 to 89-year-old group than for those in the 60 to 69-year-old group. In another article, Young[15] felt that there was some similarity in distribution of pressure gradiant and amount of atherosclerosis. Wilkins, Robert and Moses,[16] using the criterion for hypertension of a heart weight of 500 grams in men and 450 grams in women, used a system of coding in 500 consecutive autopsies and found that in men hypertension significantly increased coronary and cerebral atherosclerosis and in women significantly increased atherosclerosis in most arteries studied. They found no quantitative difference between matched male and female hypertensives. However, obese and hypertensive females were more atherosclerotic than their male counterparts. Baptista,[17] in Brazil, using the coding method of Baker, studied cerebral vessels in 322 routine autopsies. In the decades after the third, he found 22 of 34 hypertensive patients (64.6%) with atherosclerosis, whereas, in normotensives, only 18 of 163 (4.99%) had the disease. He considered patients with 2+ (B) or more as atherosclerotic. His criteria for hypertension were a pressure of 155/95 for a year, or renal and cardiac changes, or "high" blood pressure for less than a year. The rather low percentage of atherosclerosis for normotensives may be due to the fact that his criteria for hypertension might include a number of cases other investigators would have placed in the normotensive group.

Summary

A study of the relationship of hypertension to cerebral atherosclerosis, made in 2,338 consecutive autopsies, coding grossly the arteries of the circle of Willis according to the method of Baker, revealed that there were 1,711 cases with heart weight under 450 grams and 677 cases in which the heart weight was over 450 grams. The data from males and females were treated separately. The information thus gathered showed that: (1) Hypertension did quite definitely accelerate atherosclerosis in both males and females. (2) The atherosclerotic process was less prevalent in females as compared to males below the age 60 to 70, but that after this age, the female group actually had greater prevalence of atherosclerosis, especially in the hypertension group. This shift, we feel, is directly related to some endocrine factor.

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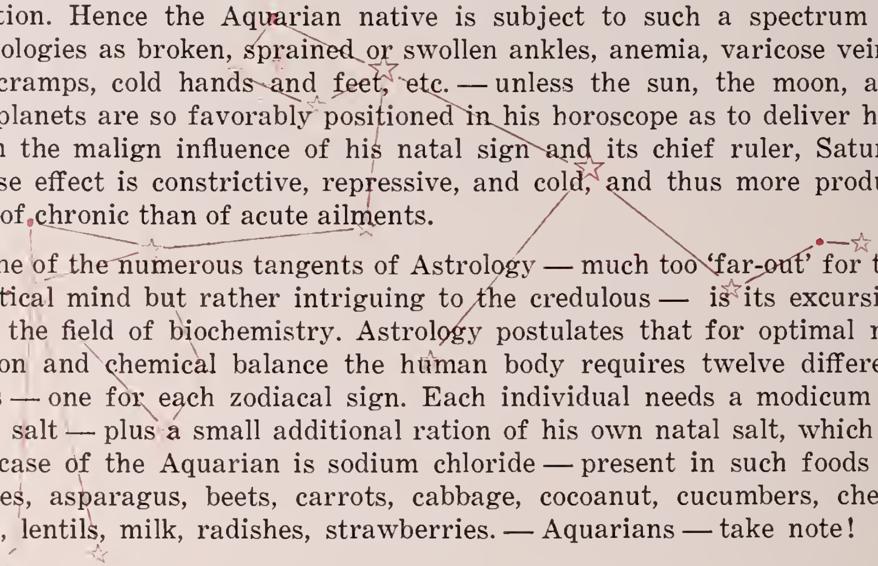
Astrology and Medicine

Aquarius — Waterbearer



Aquarius, the Water-bearer, is the sun sign from approximately January 22 to February 22, and as the eleventh sign of the zodiac Aquarius governs the lower legs and ankles, also more indirectly the general circulation. Hence the Aquarian native is subject to such a spectrum of pathologies as broken, sprained or swollen ankles, anemia, varicose veins, leg cramps, cold hands and feet, etc. — unless the sun, the moon, and the planets are so favorably positioned in his horoscope as to deliver him from the malign influence of his natal sign and its chief ruler, Saturn, whose effect is constrictive, repressive, and cold, and thus more productive of chronic than of acute ailments.

One of the numerous tangents of Astrology — much too 'far-out' for the sceptical mind but rather intriguing to the credulous — is its excursion into the field of biochemistry. Astrology postulates that for optimal nutrition and chemical balance the human body requires twelve different salts — one for each zodiacal sign. Each individual needs a modicum of each salt — plus a small additional ration of his own natal salt, which in the case of the Aquarian is sodium chloride — present in such foods as apples, asparagus, beets, carrots, cabbage, cocoanut, cucumbers, chestnuts, lentils, milk, radishes, strawberries. — Aquarians — take note!

The constellation of Aquarius can be seen October evenings on the southern curve of the ecliptic, preceded by Capricorn and followed by Pisces. Though it contains no very bright stars, the amateur astronomer can readily identify the outline of the mythical Water-bearer on any dark, clear night.

Happiness may be thought, sought or caught, but not bought. — *Mutual Moments*

Steroid Diabetes with Hypertrophy of the Islets of Langerhans

A Case Report

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THE LITERATURE on steroid diabetes contains many descriptions and illustrations of hypertrophy of the islets of Langerhans in experimental animals. However, the author is not aware of any documented cases of this finding in human steroid diabetes. Fortunately, when this case came to post-mortem examination, it was our extreme good fortune to have Dr. E. T. Bell as consultant. He reviewed the case and the following report was prepared on his suggestion and under his direction.

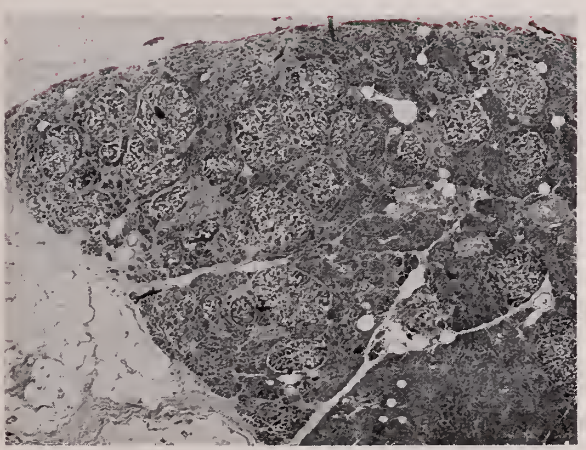

Fig. 1 — Section of pancreas showing giant islets. H & E stain magnified 25 times.

Case Report

A 63-year-old white male was admitted to the Veterans Administration Hospital, Minneapolis, Minnesota, for the first time, January 22, 1958, with the following history: The patient had had intermittent jaundice since 1947, with a severe episode in October, 1957, following a bout of pneumonia. Hemoglobin was 4.3 gm.% and a liver biopsy showed hemosiderosis. At that time he was found to have an acquired hemolytic anemia of unknown etiology, associated with hepatosplenomegaly. He was treated with prednisone 50 mg. daily, which was gradually tapered to 2.5 mg. daily. He suffered a relapse of his hemolytic condition in December, 1958. His prednisone dose was then increased to 60 mg. daily and gradually tapered to 40 mg. daily. He was then studied at the University of Minnesota Hospital and subsequently transferred to the Minneapolis Veterans Hospital.

During his stay at these hospitals the patient received an exhaustive hematological work-up which failed to disclose the etiology of his hemolytic anemia. At this time he showed an acneiform eruption on his anterior and posterior trunk, slight kyphosis of his dorsal spine, and mild peripheral edema. He continued to hemolyze, and his prednisone dosage had to be changed to meet his condition. By April 25, 1959, he had stabilized at a level between 20 to 30 mg. per day.

He was then followed in the Outpatient Clinic and did fairly well on 20 to 40 mg. of prednisone per day. On July 17, 1959, he developed a pneumonia with an accompanying severe hemolytic episode, hemoglobin dropping to 3.5 gm.%. Prednisone was then increased to 100 mg. per day, and attempts to reduce dosage below this level were unsuccessful until August 7, 1959. At that time changes of Cushing's disease were noted and one urinalysis showed a trace of sugar which had never been reported previously on this patient. Careful questioning failed to reveal any evidence of diabetes in the patient's family. Prednisone dose was gradually decreased to 5 mg. per day by September 25, 1959. At this time fasting blood glucose was 113 mg.% (normal for this laboratory at that time was 80 to 100 mg.%).

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The patient did well on 5 mg. per day until October 7, 1959, at which time he again showed evidence of hemolysis, and prednisone was gradually increased to 80 mg. per day without much effect. On November 4, 1959, a splenectomy was performed in the hope of ameliorating his hemolytic disease. He received 300 mg. of parenteral hydrocortisone on the day of surgery and daily thereafter for five days. After that, he was switched to an oral dose of 80 mg. of prednisone per day, which was gradually decreased to 20 mg. per day by November 28, 1959, and continued at the level until December 7, 1959, when the patient had another severe hemolytic episode. Prednisone was increased to 80 mg. daily and by January 4, 1960, had to be increased to 100 mg. daily. At this time the patient was also started in daily stilbestrol and testosterone for osteoporosis. On January 5, 1960, he had a sudden onset of severe back pain. X rays revealed compression fractures of T-11 and L-1 vertebrae. Back pain progressed in severity during the ensuing days, restricting the patient to bed.

During the next few days he developed a cough with basilar chest rales, and was also noted to have psychomotor depression, refusing to move or eat. He had to be tube-fed. He developed decubiti. Penicillin and chloramphenicol were started and were continued for the rest of the hospital course. Steroids were gradually decreased to 80 mg. per day. By January 26, 1960, the patient had developed a definite Cushing's syndrome with muscle wasting, weakness, ecchymoses, and decalcification of bones with multiple compression fractures. On January 31, 1960, the patient was noted to be profoundly weak and mentally depressed. On February 1, 1960, his urine sugar was 4+ with strongly positive acetone. Fasting blood glucose was 408 mg.% and CO_2 combining power was 24 meq./l. Prednisone dose was then reduced to 60 mg. per day, and a sliding scale of regular insulin based on the urine glucose levels was used to control his diabetes. He then developed a "pneumonia"; and prednisone was reduced to 40 mg. per day on February 4, 1960. He continued to deteriorate and expired suddenly while a portable X ray was being taken on February 11, 1960.

Postmortem Findings

Autopsy revealed bone-marrow and fat emboli to the lungs, pulmonary infarction with infection with Candida albicans, fat emboli to the brain, marked bilateral adrenal atrophy, multiple compression fractures of the vertebrae, fatty infiltration and hemosiderosis of the liver, coronary atherosclerosis with diffuse myocardial fibrosis, cholelithiasis, benign prostatic hypertrophy, and atrophic testes. A finding of special interest was the presence of hypertrophy and hyperplasia of the islets of Langerhans (see Figure 1).

The hypertrophied islets were somewhat irregular in outline, and in places islet cells appeared to be growing out into the surrounding acinar tissue in finger-like projectons and to be destroying the adjacent acinar tissue by compression ("mulberry" islets). The larger of the islets showed a loose sinusoidal arrangement with strands of islet cells, one or two cells thick, separated by clear areas in which thin walled capillaries were seen (see Figure 2). The islet cells were mainly polyhedral; but in certain of the larger islets a "ribbon" pattern could be seen where the cells were tall columnar with centrally placed nuclei. On H and E section the nuclei varied widely in size and depth of staining reaction. Some large dark nuclei three times the size of their fellows were noted. In the paler nuclei, single deeply stained nucleoli could be seen. Some of the islets were in close relation to ducts, and occasionally a duct was noted to be surrounded by an islet. The islet capillaries showed localized globular swellings of hyalin-like material which appeared to be inside the wall of the capillary (see Figure 3). In places the hyalin-like material appeared amorphous and in other places showed a fibrillar structure with the fibrils radiating from the center of the globule. The globules had small irregular dots of basophilic material which appeared to be calcium and stained positively with the von Kassa stain. The hyalin-like material did not give the usual staining re-

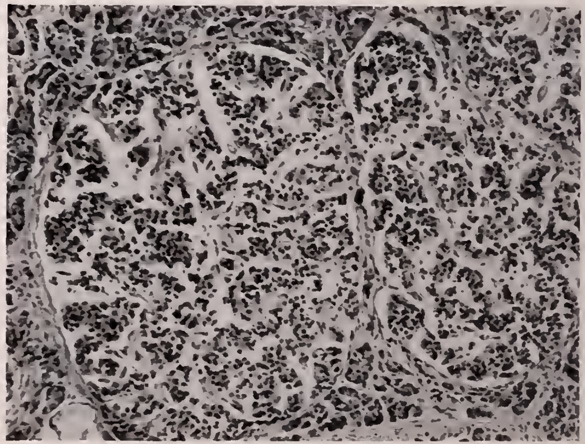

Fig. 2 — Magnification of an area from Figure 1. H & E stain. Magnified 100 times.

actions for amyloid, being PAS negative and methyl violet negative.

Islets such as described above were not seen throughout all the available sections of the pancreas, but were limited to certain areas only. The remaining islets either appeared normal or showed, in moderate degree, the more usual picture of hyalin change well recognized to occur in islets of both diabetics and nondiabetics of this age group, that is, accumulation of amorphous hyalin material in a layer of variable thickness surrounding the islet capillaries. A moderate degree of fibrosis was present in the form of a capsule around some of the islets. The structure of the islets was well preserved, and it is felt that the changes observed could not be accounted for on the basis of postmortem change. No hydropic change, lymphocytic infiltration, or islet hemorrhage was noted.

Gomori's chrome alum hematoxylin stain showed marked degranulation of the beta cells of the hypertrophied islets and a lesser, though still pronounced, degranulation of the beta cells of the nonhypertrophied islets. The degranulation was present in what has been described as a "discontinuous" pattern, that is, scattered beta cells seemed to have a full complement of granules; many had a few granules; and many had none at all. Occasional islet cells that appeared to be alpha cells were seen in almost all the islets, but due to the widespread degranulation, an estimation of their relative proportion was unreliable.

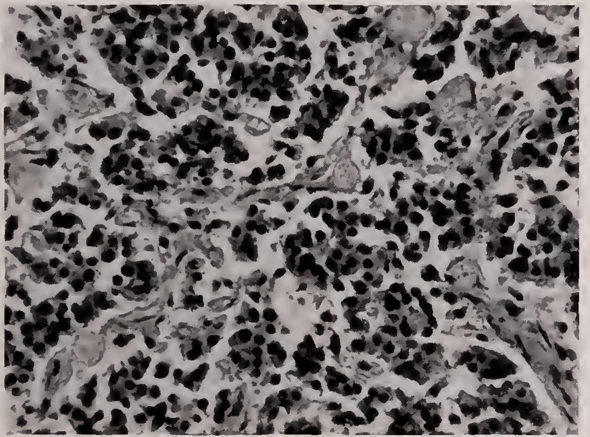

Fig. 3 — Magnification of islet from Figure 1. Note nodular swellings on capillaries in islet. H & E stain magnified 200 times.

Discussion

To demonstrate the degree of hypertrophy of the islets of Langerhans in this case the following was done: 90 consecutive islets were measured with a micrometer in their longest and shortest diameters in an H and E section of an area a few cm. from the tail end of the pancreas. Serial sections were not done. The area of each islet was determined by using the formula for an ellipse (long radius x short radius x pi). Blocks were taken from comparable areas of pancreases obtained at autopsy from five middle-aged nondiabetic white males selected at random, with no history of pancreatic disease. Fifty consecutive islets were measured in each pancreas in the same manner as in the abnormal pancreas. No pancreatic abnormality was noted in any of the five control pancreases. Table 1 gives the results of these measurements and Table 2 gives the frequency distribution of islets by size in the six pancreases. The most striking thing to be noted from the Tables is that approximately 17% of the islets in the abnormal pancreas measured over 75,000 sq. micra, whereas none of the islets in the control group were of this size. The above was done with the knowledge that there are many objections to the statistical validity of such a procedure, and for this reason no statistical analysis of the data will be attempted. Serial sections or whole gland (head to tail) sections were not done, as the whole gland was not available for study.

Numerous authors have measured islets of Langerhans, but unfortunately the usual method has been to measure only the longest axis. Those who have used this method generally agree that any islet whose greatest diameter is over 400 micra is hypertrophied.[1] By this criterion, 12% of the 90 measured islets in this reported case would be considered to be hypertrophied. If serial sections had been made, I feel certain that this percentage would be increased. The largest diameter observed in this case was 780 micra.

Giant islets are described early in the

TABLE 1
Comparison of Islets in H & E Sections from Reported Case and 5 Controls

	Average Islet (calculated)		Largest Islet (observed)		Smallest Islet (observed)	
	Area (sq. microns)	Dimensions (microns)	Area (sq. microns)	Dimensions (microns)	Area (sq. microns)	Dimensions (microns)
Control 1	8,335	80 x 110	23,772	161 x 188	1,319	28 x 60
2	11,642	97 x 122	49,072	220 x 284	726	28 x 33
3	10,587	95 x 128	39,716	196 x 258	2,395	50 x 61
4	8,947	86 x 119	33,628	192 x 223	2,398	43 x 71
5	18,211	125 x 158	74,223	298 x 327	1,319	40 x 42
Reported Case	54,446	159 x 215	269,696	583 x 589	592	26 x 29

TABLE 2
Frequency Distribution of Islet Areas in Reported Cases and 5 Controls

	Percent of Islets Control Pancreases					
Area (sq. microns)	1	2	3	4	5	Abnormal Pancreas
0 - 25,000	100	90	98	96	80	62.2
25,000 - 50,000		8	2	4	20	16.7
50,000 - 75,000		2				4.4
75,000 - 100,000						5.6
100,000 - 125,000						3.3
125,000 - 150,000						2.2
150,000 - 175,000						2.2
175,000 - 200,000						
200,000 - 225,000						2.2
225,000 - 250,000						
250,000 - 275,000						1.1

course of naturally occurring human diabetes as well as steroid diabetes in experimental animals. This case bridges the two groups in that it exhibits giant islets in steroid diabetes in a human being. It is generally felt that islet hypertrophy represents an attempt on the part of the pancreas to compensate for increased insulin demand, and the fact that the giant islets show degranulation of their beta cells tends to support this. The evidence supporting the theory that islet hypertrophy is secondary to increased functional demand has been reviewed elsewhere.[2]

All of the morphologic changes described in the islets of Langerhans in this case have been described in hypertrophied islets due to other causes and in other animals, although very rarely are they this florid.

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Life is not lost by dying! Life is lost minute by minute, day by dragging day, in all the thousand, small, uncaring ways. — *Stephen Vincent Benet*

Revived Interest in Renal Heterotransplantation

Present Status in 1964

E. T. Bell — Brilliant Scholar, Devoted Professor, Endearing Friend; His presence among us enlarged our vision and enriched our lives; His greatness grows larger as he lives longer in our memories.

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SUCCESSFUL TRANSPLANTATION of a healthy vital organ to replace a diseased one has been a long-sought dream of mankind. Sporadically over the centuries daring investigators using crude techniques and lacking firm scientific knowledge have attempted various kinds of heterografts between lower animals. In all early efforts these novel feats were failures; but the hope of ultimate success from this form of surgery still lures modern investigators to renewed efforts. Most transplantation work has been directed toward the kidney. Early investigators soon realized the value of experiments performed with "paired" vital organs capable of clear-cut functional evaluation.

Not until the beginning of the 20th century, however, did serious work begin which can be considered the forerunner of modern attempts at renal heterografting. In 1905 Princeteau implanted two pieces of a ribbit kidney into a nephrotomy performed in the kidney of a child, but was unable to establish evidence of any function of this tissue.[1] Jaboulay in 1906 transplanted kidneys from both the pig and the goat into humans but found no evidence of function of these heterografted organs.[1] In 1910 Unger performed a transplant of a subhuman primate kidney into man and found no function of the organ upon critical evaluation.[2] Neuhof in 1923 treated a patient suffering from renal failure secondary to bichloride of mercury poisoning by transplantation of a lamb kidney, and this patient died nine days later without satisfactory function of the transplanted organ.[1]

A long hiatus then ensued in this type of replacement therapy until February, 1963, when the author and his colleagues on the transplantation team at the Hennepin Coun-

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ty General Hospital, Minneapolis, Minnesota, transplanted the kidney of a 48-pound Kenya baboon (Papio doguera) into the thigh of an Indian woman suffering from renal failure.[3] This patient was rejecting a previously implanted renal homograft, and the heterograft was attempted as a final lifesaving measure. It is singularly important that this baboon-to-man heterograft functioned immediately upon vascularization in the recipient and excreted significant quantities of urine (up to 3000 cc. daily) for four and one-half days. Function suddenly ceased, however, when the transplanted renal artery became thrombosed, and the kidney was removed successfully at another operation with preservation of the patient's femoral vessels. The patient died, however, several weeks later of uremia.

For many decades there was a consensus among investigators in the transplantation field that heterografted tissue would immediately be rejected by a human recipient. The basis for this opinion was the common experience of an immediate rejection when heterografts were performed between lower animals.

The use of a kidney from the Kenya baboon in the author's patient was a fortunate choice and a logical outgrowth of earlier work by the Minneapolis group which had demonstrated successful long-term extracorporeal storage of the baboon kidney at 5-10° C.[3,4] Autografts of such cooled and stored baboon kidneys had functioned normally for several years following contralateral nephrectomy in these animals. In addition, Telander (Minneapolis group) had shown that the baboon kidney could be maintained successfully outside the body at normal temperatures for periods up to eight hours in a pump perfusion apparatus and be reimplanted with successful prolonged function after contralateral nephrectomy.[5]

By early 1963 the baboon as an experimental animal had incited considerable interest among numerous investigators, since these animals had been found to develop atherosclerosis in about 10% of older males (while living in their normal habitat in Kenya, East Africa).[6,7] Physiologically there appeared to be similarities between man and this subhuman primate which made him a reasonable candidate for donation of a vital organ such as a kidney.

During October, 1963, Reemtsma and the transplantation team at Tulane University transplanted both kidneys of a 25-pound rhesus monkey to a 32-year-old woman, and the immediate function of the kidneys was satisfactory.[8] They were removed 10 days later, however, when function failed, and the patient subsequently died of pneumonia and gastrointestinal hemorrhage in spite of treatment on an artificial kidney. During November, 1963, the Tulane group transplanted both kidneys of a large chimpanzee to a 44-year-old man suffering from renal failure secondary to glomerulonephritis. This patient was treated during two episodes of early rejection of the heterografted kidneys by the addition of irradiation and steroids to the basic immunosuppressive program (Imuran). The patient died nine weeks after surgery of pneumonia. The Tulane transplantation team has continued to use the chimpanzee as the donor in several additional renal heterograft operations, and, at the time of this writing, at least one patient has survived for a period of four months with satisfactory renal function.

The Denver Collaborative Effort

During December, 1963, and the early months of 1964 a series of six patients received kidney transplants from Kenya baboons in a collaborative study between the transplantation team in Denver, Colorado, and the Hennepin County General Hospital in Minneapolis. The six patients selected for this study were all terminally ill with renal failure and each lacked an adequate human donor (close relative) for a living homograft.

Previously Starzl and the Denver transplantation team had performed a remarkably successful series of renal homografts and had demonstrated the importance of several new thoughts basic to success in this field. First, they had clearly shown the value of obtaining kidneys from living donors with complete control over the entire transplantation operation to assure a short ischemia time of the grafted organ. Second, they had demonstrated clearly the value of steroids as an adjunct in the immunosuppressive program following transplantation. Third, they had shown the importance of genetic similarity as evidenced by matching blood groups between the donor and the recipient, preferably as blood relatives. And fourth, they established the benefit of concomitant splenectomy and bilateral nephrectomy at the time of the homograft placement.

The first patient in the heterograft series, a 41-year-old man, received two heterografted kidneys from a baboon, one in each groin, and the organs functioned well for 18 days. Following several pulmonary emboli from thrombophlebitis in the legs he died 24 days after surgery of an abscess in the right lung. At autopsy the grafted kidneys compared favorably to homografted kidneys at a similar time interval. Splenectomy and bilateral nephrectomy were performed at the time of these renal heterografts, as in previously performed homograft cases.

The second patient, a 45-year-old man suffering from glomerulonephritis, received both kidneys from a Kenya baboon in one tandem preparation, using the aorta and vena cava for anastomoses to the right iliac vessels. Immediate postoperative function was excellent, with a diuresis during the first 24 postoperative hours of 29 liters of urine. The patient had the left lower lobe of his lung resected successfully for an abscess but died of anuria 30 days after the transplantation. The third patient was a young man of 18 years of age suffering from glomerulonephritis, who survived 58 days following transplantation of two Kenya baboon kidneys as one tandem preparation. This patient gained weight after the surgery and had apparent good function of the grafted organs for a period of about 40 days before it was apparent that the heterografts were undergoing serious deterioration. A subsequent homograft was tried in this patient, but he finally succumbed of sepsis.

TABLE I

Patient No.	Patient's Blood Group	Baboon Blood Group
1	A	A
2	O	B
3	AB	B
4	B	B
5	O	AB
6	O	AB

The fourth patient, a young man of 20 years, received two baboon kidneys as a tandem preparation, but immediate function was not as satisfactory as in the previous patients. These kidneys were in situ for 49 days, but the patient continued to have a high blood urea nitrogen, and dialysis was needed during the sixth post-operative week. This patient also received a homograft from a nonrelated donor after the heterografted organ had been removed, but he eventually died of sepsis. The fifth patient was a man of 36 years of age who lived 19 days following the renal heterograft, though the kidneys were clearly rejected. The sixth patient, a man of 31 years of age lived 46 days following renal heterografting, but the renal function was not satisfactory at any time, the patient continuing to have a blood urea nitrogen in the range of 100-110 mg.%.

Importance of Genetic Similarities

Critical review of the homograft experience by the Denver team indicates a higher degree of long-term success following homografts between blood relatives with identical major blood groupings. Compatible blood-group matches between a nonrelated human donor and the human recipient does not give as good long-term results. The question of blood groups in the subhuman primate obviously became of great interest.

Wiener and Moor-Jankowski have shown during recent years that the chimpanzee has major blood groups 0 (12%) and A (88%), and the baboon has blood groups A, B and AB.[9] As far as testing for the A B O blood groups is concerned, these investigators believe the gorilla is the most different of the subhuman primates from man and is closer to the monkeys.[10] The chimpanzee and the baboon appear to be the most likely subhuman primate candidates for organ grafting at this time.

In the collaborative Denver study it is of interest to correlate the final functional results with the blood groups chosen for the human-animal pairs; these blood groupings are shown in Table 1. From this table it is apparent that a compatible blood-group match existed for patients 1, 3, and 4, and a mismatch for patients 2, 5, and 6. Although all of these heterografted baboon kidneys were ultimately rejected by a violent immune reaction, the immedite post-operative function was better in those situations with compatible blood group matching; also the patients survived for somewhat longer periods with better renal function.

Experience in the grafting of chimpanzee kidneys into humans by the Tulane group has shown comparable results, with immediate rejection of a kidney from a type A chimpanzee after transplantation into a type O human. This patient was immediately regrafted with a chimpanzee kidney from an O blood type animal with immediate successful function.

Immunological Considerations

The plan of immunosuppressive therapy which has held most promise in homografts between humans, has been applied in the heterograft experience. The spleen and both kidneys of the recipient were removed at the time of the transplantation. Suppressive therapy with azathioprine (Imuran) was begun in the heterograft patients in the collaborative study four to eight days prior to surgery. Steroids in the form of prednisone were used beginning with the first preoperative day. Irradiation therapy to the grafted organ (as introduced by Hume) was also used when early signs indicated the likelihood of an impending rejection crisis. These signs are now recognized as slight fever, decreased urine output, decreased sodium excretion, and tenderness over the grafted organ. Intensive immunological studies have been performed on the sera of these patients and are to be reported elsewhere.

In the case of the baboon heterografts repeated rejection crises were encountered and intensive suppressive therapy was necessary in order to maintain an effective function of the grafted kidneys. It appears at this time that post-operative function of successfully grafted chimpanzee kidneys (with compatible blood-group matchings) is better than in similar cases with the baboon, and somewhat less vigorous immunosuppressive therapy is needed for control. The use of potent reticuloendothelial depressant drugs heightens the difficulties in the control of infections, but in the case of homografts infection problems can be overcome. We can only hope, at this time, that success in the heterograft field can be achieved to a similar degree in the immediate future.

The Donor Problem

Although the homotransplantation of kidneys must still be considered an experimental technique, it is now apparent that reasonable long-term success can be achieved with genetically related donor-recipient individuals of similar blood groups. Paramount in the minds of all investigators is the great difficulty attending procuremnet of satisfactory organs.

Successful techniques are now at hand for adequately storing kidneys (both subhuman primate and human) for a reasonable number of hours following procurement. Cadavers as a source of kidneys pose many problems.

Only accident victims or patients suffering from cerebral vascular accidents can ordinarily be used as cadaver donors. It is important that the grafted kidney be from a younger individual, preferably below 35 years of age. This immediately narrows our field to the young accident victim wherein the kidneys have not been damaged and there is no degree of shock for more than a few minutes prior to removal of the organ. The difficult problems of securing permission for removal of the kidneys under emergency conditions quickly following death are obvious.

In addition to the difficulties of obtaining adequate cadaver kidneys we now realize the necessity of genetic similarity. Results have not been as satisfactory in patients receiving homografts from nonrelated donors, even with compatible blood-group matchings. The results are, however, in most instances better than the use of cadaver grafts.

The value of ultimate success with heterografted organs is obvious. There is every justification at this time for continued serious effort in this field in those laboratories equipped to cope with these problems. Undoubtedly new forms of suppressive therapy will be developed and the further use of heterografts under newer conditions is, I believe, justified under properly controlled conditions.

We have an obligation to further probe the boundaries limiting success in the field of organ grafting. Empirical clinical research may well increase survival of patients with homografted kidneys and other homografted organs such as the lung and pancreas. Complete understanding of the pathophysiology of the immune processes involved in tissue and organ grafting may come slowly in spite of broad research programs on basic mechanisms. Our critically ill patients, in need of new vital organs, deserve our best continuing clinical efforts tempered with judgment and concern for scientific accuracy.

Summary and Conclusions

During 1963 and 1964 we have witnessed a resurgence of interest in the potential for renal heterografting between subhuman primates and humans. Several well controlled studies have been performed and detailed observations made. It is now apparent that among the subhuman primates the most likely animal for this use is the chimpanzee.

A more intensive program of immunosuppressive therapy is required in attempting control of renal heterografts at this time than is currently needed for control of rejection in patients with renal homografts. To date all heterograft attempts using the Kenya baboon as the donor have failed. A minimal degree of success has attended the use of the chimpanzee.

The fact that a significant series of heterografts has been performed both with the chimpanzee and the baboon as donor and that these grafts have functioned for varying periods of time without immediate rejection is a point of real importance for the future. Persistence in basic studies can reasonably be expected to bring further advances and improvements in immunosuppressive methods. In spite of the high percentage of failures in the recently performed clinical cases we are definitely further along the road to success than we were two or more years ago.

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Poisons

There is no form of lead-poisoning which more rapidly and thoroughly pervades the blood and bones and marrow than that which reaches the young author through mental contact with type-metal. — *Oliver Wendell Holmes*

Effect of Heparin*

• On
• Blood
• and
• Tissue
• Lipids

"I did a little arbeit . . ." — E. T. Bell

THIS STUDY was undertaken to determine the comparative amounts of fat that would accumulate in various organs after a large continuous infusion of a stable fat emulsion, and to observe the effect of a large dose of heparin on such accumulations.

Methods and Materials

Infusion Procedure

Sprague-Dawley male rats ranging in weight from 240-490 grams were used. Lipomul (Upjohn)[1] or saline was infused continuously through a polyethylene catheter in the tail vein while the rats were immobilized in a restraining cage. The animals were not pre-fasted. No food or water was given during the infusion period. The infusion was at a rate of approximately 2.0 ml. per hour, and was continuous for 1, 2, 4, 8, 12, 18, 24, or 48 hours. Six rats were run at each of these 8-time intervals. For purposes of analysis the animals were later grouped to form 5-time intervals: 1-2 hrs., 4-8 hrs., 12-18 hrs., 24 hrs., and 48 hrs. The fat injection rate was 0.3 gm. per hour or 7.2 gm. per day. The approximate amount of fat received by the animals at each of the 5-time intervals was: 1-2 hrs., 1-2 gm./kilo; 4-8 hrs., 5gm./kilo; 12-18 hrs., 10-15 gm./kilo; 24 hrs., 20 gm./kilo; and 48 hrs., 40 gm./kilo.

The rats were divided into three groups as follows: 1. Saline controls, 2. Those receiving fat only, 3. Those receiving fat plus injections of heparin. Forty-eight hours is just about the limit of tolerance of rats for such continuous infusions of Lipomul. The rats of group 2 that went 48 hours were in poor shape at time of sacrifice. Diarrhea was prominent at 24 hours. In the third group, 2 mg. aqueous heparin (approximately 6 mg./kilo) was given intravenously at the start of the infusion, and 3 mg. Depo-heparin (Upjohn) (approximately 9 mg./kilo) was given subcutaneously at the start of the infusion and after 24 and 41 hours in the rats whose infusions continued for 48 hours.

The animals were weighed before and after the infusions. Nearly all lost some weight.

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Following Continuous Infusions of Fat in Rats

After 48 hours this varied between 3% and 14% of body weight.

At the conclusion of each infusion period each animal was anesthetized with ether and sacrificed by exsanguination. The entire procedure took place within 5-10 minutes after the infusion was stopped. The blood was allowed to clot and the serum frozen for later analyses. The liver, spleen, kidneys, and lungs were removed, weighed, one piece taken for histologic examination, and the rest quickly frozen for later chemical analysis. The tissues and serum were kept frozen (−20° C) for 9-12 months before the chemical analyses were made.

Preparation of Tissue for Analysis

The partially defrosted tissue was cut into small pieces with a razor blade, then allowed to defrost completely, after which it was homogenized. A medium-sized Teflon homogenizer was used for liver and kidney, a small ground glass one for spleen and lung. The homogenized tissue was transferred to weighing flasks and the net weight recorded. Acetone was added to the flask immediately and the contents mixed thoroughly until nearly all of the tissue was in suspension. Then the acetone was evaporated completely. The flasks were placed in a vacuum desiccator overnight and dried.

The next morning the vacuum was released and the flasks reweighed, after which they were replaced in the vacuum desiccator for two more hours and then weighed again. This procedure was repeated if necessary until the dry weight was constant. It was rarely necessary to repeat the procedure. With few exceptions tissue moisture varied from 64-77%. Chloroform-methanol (2:1) was added to the dried tissue and the tissue lipids extracted. The filtrate was used for analysis for triglycerides, cholesterol, phospholipids, and free fatty acids. Results were expressed as mg. per gram of dry weight for TG, TC, and PL, and as μeq. per gram of dry weight for free fatty acids. In the case of blood, the frozen serum was thawed and used directly. Results were expressed as mg. per 100 ml. for all but free fatty acids which was expressed as μeq. per ml.

Methods of Lipid Analysis

Triglycerides were measured by the formaldehyde chromotropic acid method of Van Handel and Zilversmit,[2] free fatty acids by the heptane thymol blue method of Dole.[3] Phospholipid phosphorus was measured by the phosphomolybdate method of Fiske and Subbarow,[4] cholesterol by the p-toluene sulfonic acid method of Turner and Eales.[5]

Presentation of Results

The vertical bars in the graphs record the mean values for each group at each time interval, and the vertical line through the tip of each bar gives the range of values observed (in 2-4 rats). If no vertical line is present the values happened to be the same. An asterisk above the bar indicates that data on only one animal was available. The open bars represent the saline controls, the diagonal-lined bars those receiving fat infusions only, and the stippled bars those receiving fat infusions plus heparin injections.

Results

Tissue Lipids

Figure 1 portrays the results of triglyceride or fat analyses on liver, spleen, lung, and kidney. Over a period of 48 hours, the triglycerides increased progressively and markedly in the liver, spleen, and lung, but only slightly in the kidney. The amount in the liver, spleen, and lung was similar, being about 300 mg. per gram of dry weight at 48 hours. The kidney contained about ⅓ as much. With the addition of heparin, a reduction in tissue fat deposition becomes apparent at 24 hours, and there is no difference from the saline controls at 48 hours. The slight increase in triglycerides in the livers of the saline controls is probably related to the fact that they received no food. Figure 2 shows the histologic appearance of the liver and

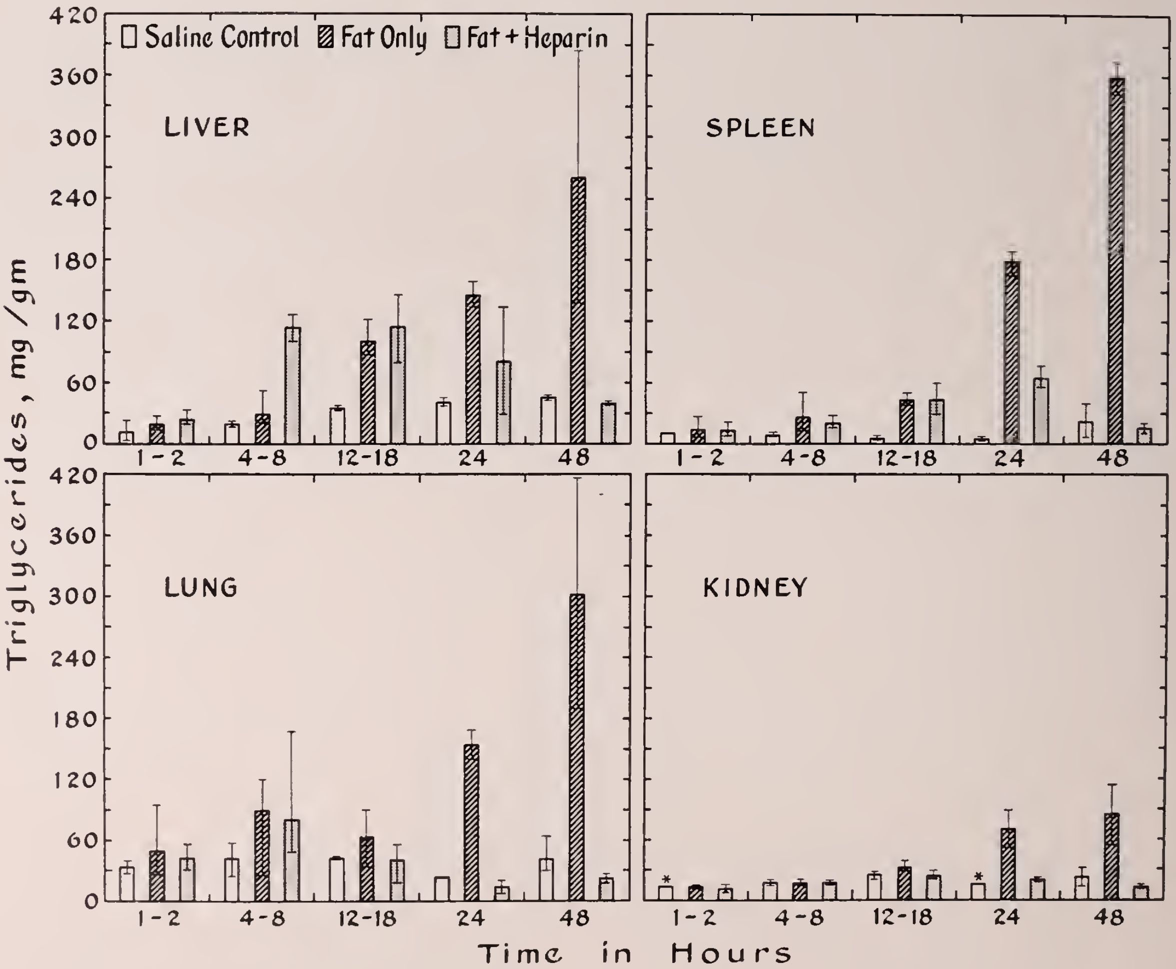

Fig. 1 — Triglyceride content of liver, spleen, lung, and kidney at various time intervals.

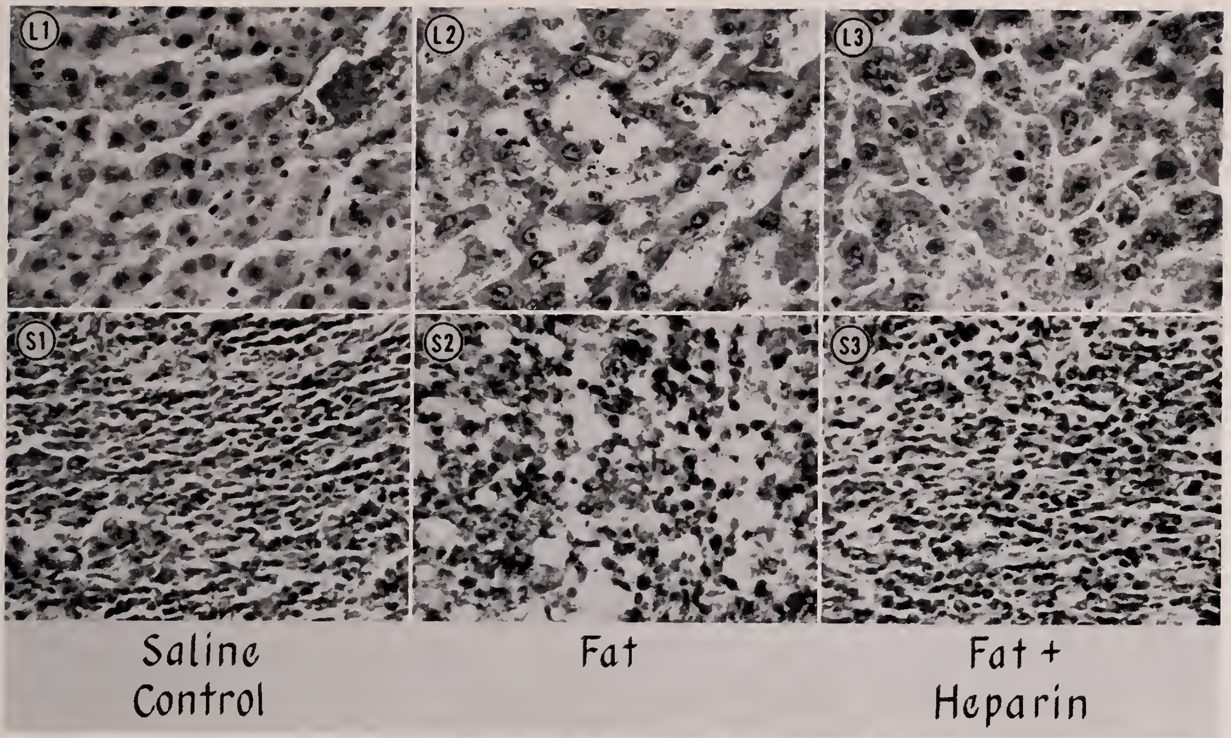
L1
L2
L3
S1
S2
S3
Saline Control
Fat
Fat + Heparin

Fig. 2 — Histologic appearance of liver and spleen in rats receiving saline, fat, and fat plus heparin over a 48-hour period.

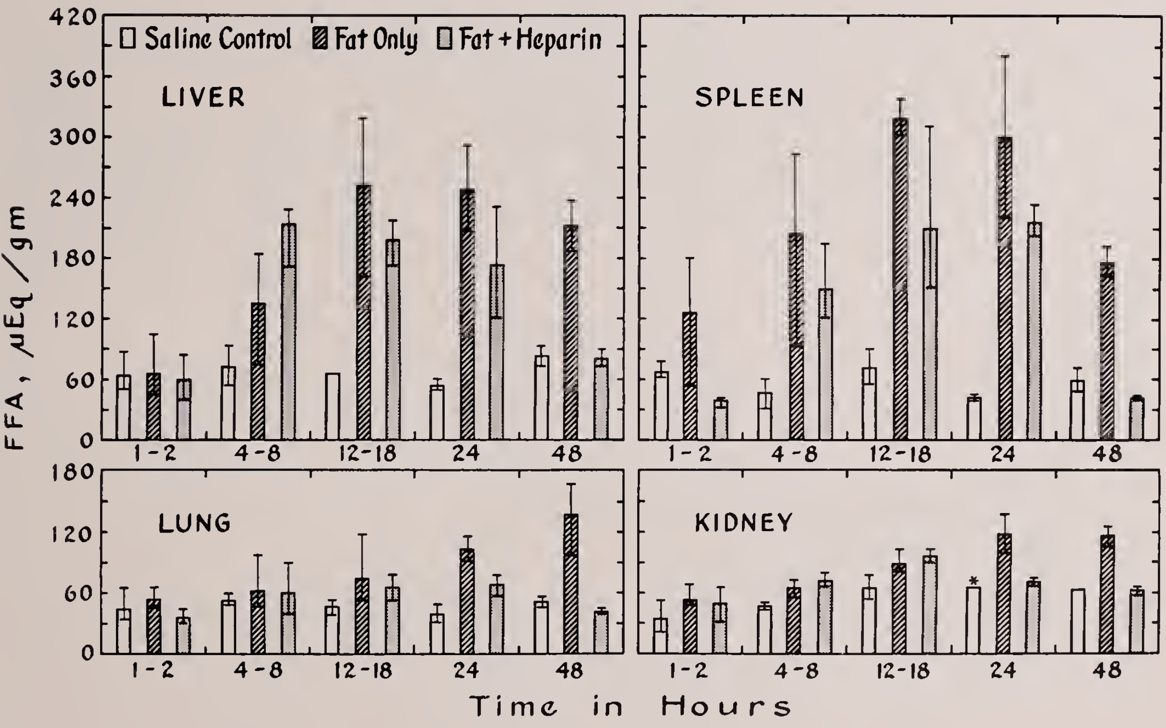

Fig. 3 — Free fatty acid content of liver, spleen, lung, and kidney at various time intervals.

spleen at 48 hours in rats receiving saline (1), fat (2), and fat plus heparin (3). The von Kupfer cells of the rat receiving fat only are distended with fat (L2), and the spleen is likewise greatly distended with fat (S2). The histology of the animal receiving fat plus heparin is more like that of the saline control.

The results of the analyses for free fatty acids are shown in analogous fashion in Figure 3. Free fatty acids in the liver and spleen are similar in amount, and the peak values are observed at 12-24 hours. The values in lung and kidney are only 2/5 as high and the peak is reached in 24-48 hours. With heparin, a decrease in the accumulation of free fatty acids becomes apparent in the liver and spleen by 12 hours, and in the lung and kidney by 24 hours. At 48 hours there is again no difference from the saline controls.

As can be seen in Figure 4, the tissue content of total phospholipids was essentially similar among all three groups, there being no effect from the fat infusions. Liver and kidney contain slightly more phospholipid than do spleen and lung.

The tissue content of cholesterol (Figure 5) was also essentially similar among all three groups, with perhaps a slight increase in liver and spleen cholesterol at 24 and 48 hours as a result of the fat infusions. Liver cholesterol is in general slightly lower than that of the other organs.

Blood Serum Lipids

The changing concentrations of all four

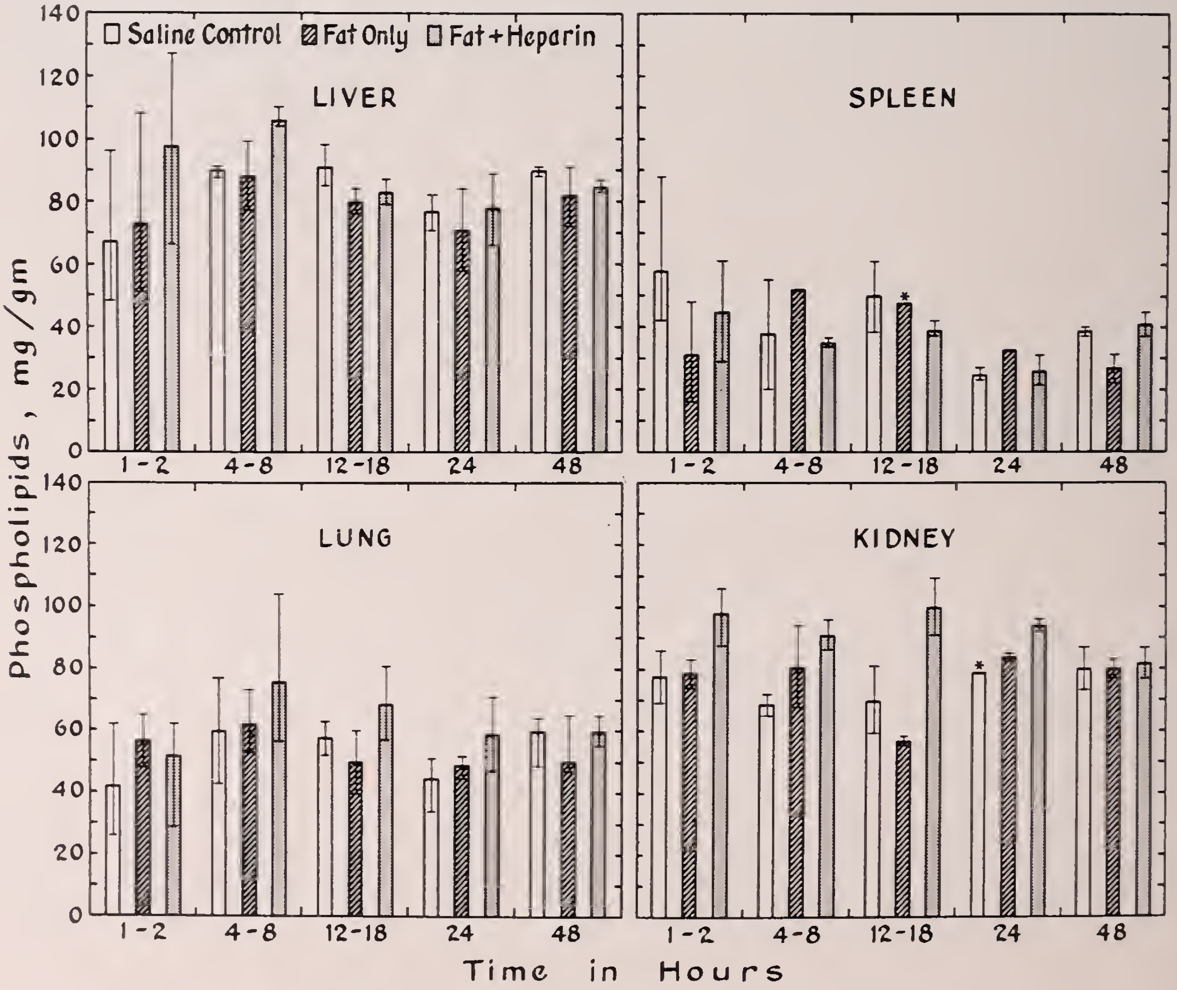

Fig. 4 — Phospholipid content of liver, spleen, lung, and kidney at various time intervals.

lipids in the blood are shown in Figure 6. The serum triglycerides rose to a peak in 24-48 hours reaching concentrations in the range of 5000-10000 mg. per 100 ml. With the addition of heparin, the rising serum concentration lagged behind and then decreased at 24 hours, being no different from the saline controls at 48 hours.

Serum free fatty acids rose to an earlier peak at 12-24 hours after the fat infusions, reaching levels of 7000-8000 μeq. per liter. With the addition of heparin the increase in free fatty acids was even greater, up to 10000 μeq. per liter, between 4 and 18 hours. Then there was a rapid fall-off, with control levels approached by 48 hours.

Unlike the tissues, serum phospholipids rose progressively to a peak at 24-48 hours, with concentrations approximately 6 times normal. With the use of heparin, the concentration decreased at 24 hours and was at control levels at 48 hours. Serum cholesterol changed similarly. With fat infusions the peak concentration reached at 24-48 hours was about 4-5 times normal. With the addition of heparin, the concentration decreased at 24 hours and reached control levels by 48 hours.

Discussion

This study has shown that continuous infusion of a stable cotton-seed fat emulsion to the limits of tolerance in rats results in a variable increase in blood and tissue lipids. Triglycerides increased roughly 150-fold in the blood serum, 20-fold in the liver and spleen, 10-fold in the lung, and 6-fold in the kidney. Free fatty acids increased approximately 9-fold in the serum, 4-fold in the liver and spleen, and 3-fold in the lung and kidney.

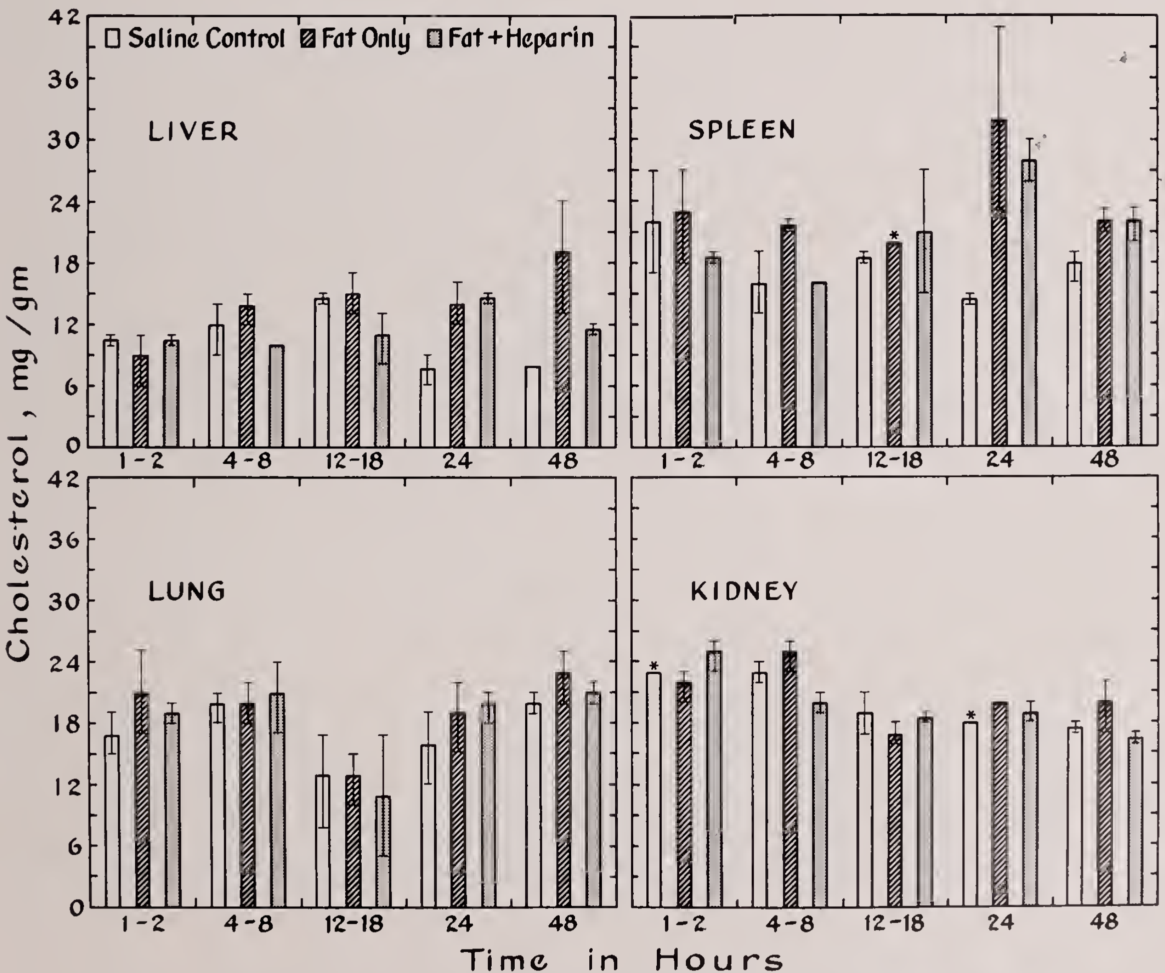

Fig. 5 — Cholesterol content of liver, spleen, lung, and kidney at various time intervals.

Phospholipids and cholesterol did not increase in the tissues but increased 8-fold and 5-fold respectively in the serum. A large dose of heparin prevented the continued accumulation of all the lipids in the blood and the tissues, taking about 48 hours for full effect.

The accumulation of fat in the liver, spleen and lung after intravenous administration of fat was recorded long ago. Eckles,[6] in a very interesting thesis, critically reviewed the early experiments that dealt with the consequences of parenteral administration of various lipids to animals. Emulsions used at that time were generally unstable.

During the period of development of the modern fat emulsions in the 1950s, Geyer and co-workers[7-9] infused coconut and corn oil emulsions into rats in the amount of 2-½-10 gm./kilo, and observed the accumulation of fat in the liver, spleen, and lungs. Fat accumulation was extensive with unstable emulsions and moderate with stable emulsions. With stable emulsions, the excess fat was gone from the organs in about 24 hours. In other experiments, they demonstrated that most of the clearing of fat from the blood was by the liver and spleen, and that blockade of the reticuloendothelial cells did not alter the rate of removal from the blood, though it prevented deposition of the fat in the RE cells.

A little work has been done on the effect of heparin on the fate of infused fat. Grossman and Strub[10] gave 3.3 gm. of fat per kilo to rats, using sesame oil. They found that heparin intravenously in a dose of 10 mg./kilo speeded up the removal of the fat from the blood and decreased the accumulation of

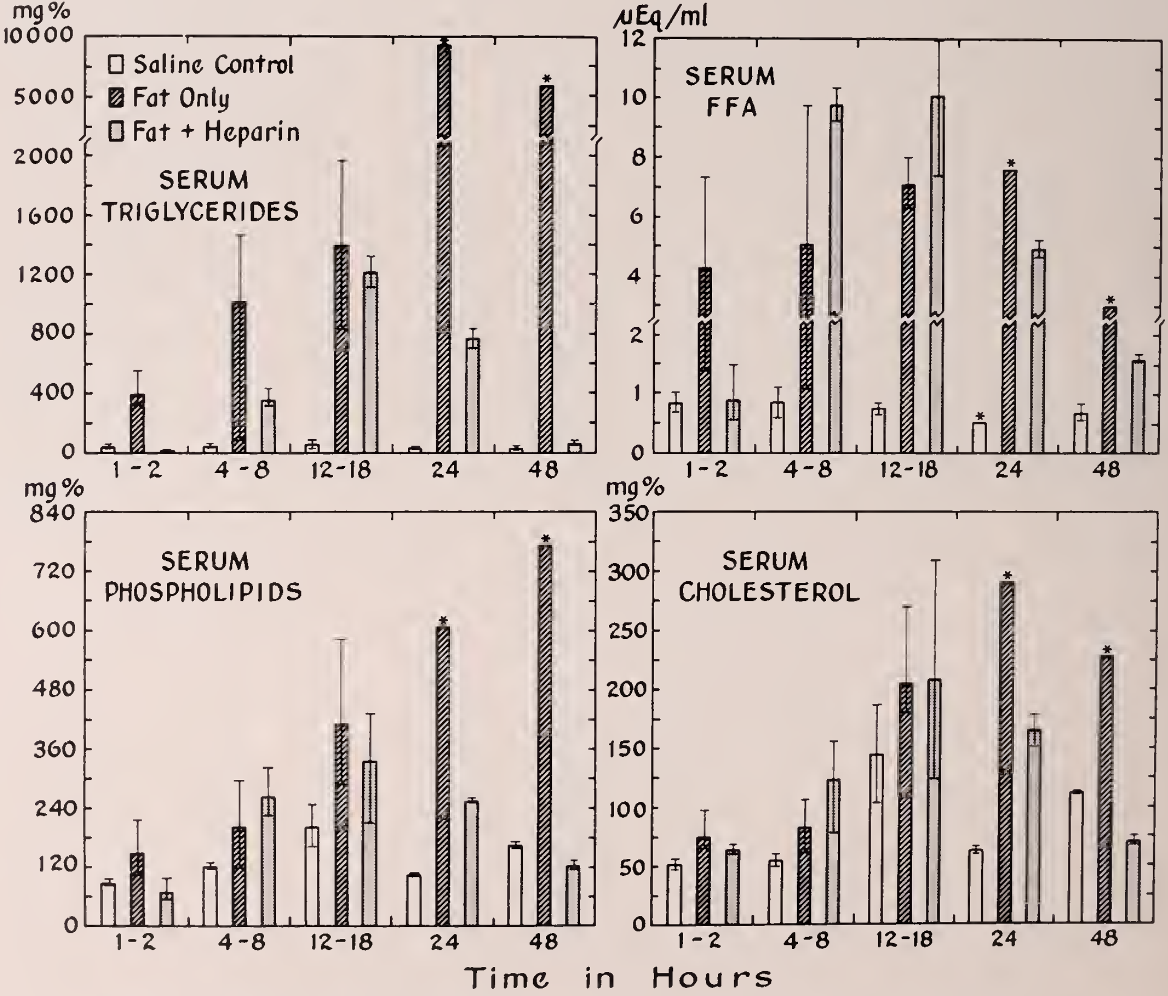

Fig. 6 — Concentrations of triglycerides, free fatty acids, phospholipids, and cholesterol in the serum at various time intervals.

fat in the liver and spleen, particularly the latter. With C^{14}-labeled soybean oil at a dose of 1 gm./kilo, Becker, Rall and Grossman[11] found that heparin decreased the blood and splenic content of labeled lipid, while increasing the muscle content and the respiratory CO_2. Von Brand, Drescher, and Zollner[12] confirmed these observations with C^{14}-labeled tripalmitin. Meng and Edgren[13] presented evidence recently in dogs that heparin causes a marked increase in the plasma free fatty acids after an infusion of fat and that the fatty acids result from intravascular lipolysis. Thus heparin seems to enhance the uptake of fat by the tissues as well as the metabolic processing of the fat.

Relatively few studies of the fate of intravenously-injected fat have been made and variations in the physical and chemical nature of the emulsion, dosage, duration of the infusions, and the use of heparin make comparisons difficult. Our study was distinguished by the use of a highly developed stable cottonseed oil emulsion, administration by continuous infusion of very large amounts of fat to the point of maximum tolerance, the use of continuously acting heparin in large dosage, and quantitative chemical analyses of the major classes of lipids in the various tissues of known importance. Despite differences in many respects, our chemical studies following large amounts of fat support previous tracer studies with radioactive-labeled fat, which indicated that heparin increases both the clearance of infused fat from the blood and the metabolic disposition of the fat in the tissues. However, it is not likely that the huge quantities of fat that were infused were simply redistributed in the tissues (muscle, bone, etc.) or metabolized to CO_2 and water.

The average 300-gram male rat requires approximately 113 calories per kilo per day or 34 calories per rat. Our rats, which were immobilized, received as much as 63 calories per day, about twice the daily caloric requirement, and still lost weight. The recent observations of Wilkins[14] offer an explanation for the discrepancies. Wilkins observed that Lipomul appeared in the duodenum within minutes after an intravenous infusion and that at the end of 30 minutes approximately one half the fat could be recovered from the intestinal contents. Unfortunately we did not examine the intestinal contents of our animals, despite the occurrence of diarrhea, and missed this observation. Inert particles less than 0.1 μ are readily excreted into the bile, since Juhlin[15] observed that spheres of polymethylmethacrylate of such size appeared in the bile of rabbits within minutes of their injection. Apparently excessive fat is handled like the inert particles.

It seems quite likely that a large amount of the fat we infused was excreted via the intestine. What effect heparin might have had on such excretion remains an interesting question. The unexcreted fat was probably broken down as a result of lipolysis stimulated by heparin, and the fatty acids redistributed in the tissues or metabolized.

Our original interest in this question stemmed from an experience[1] with a patient who received approximately 100 gm. of fat per day as Lipomul for nine weeks, and who had no reaction while he received the fat and also an injection of 100 mg. of heparin each week. After discontinuing both, he had a severe reaction, and we wondered if the delay in onset of the reaction could have been attributable to the small amount of heparin he had received. During the period of the "overloading syndrome" his serum triglycerides rose higher than during the period of the infusions. It seems likely in the light of our present results that concomitant use of heparin in sufficient dosage at the time of fat infusions will significantly alter the toxic effects.

Summary

Infusion of a large amount of a stable cottonseed oil emulsion into rats resulted in the accumulation of large amounts of triglycerides in the liver, spleen, and lung; and of free fatty acids in the liver and spleen. Phospholipids and cholesterol did not increase significantly in these organs. All four lipids accumulated in the blood as the infused amount of fat increased. A large dose of continuously acting heparin prevented the continued accumulation of lipids in these tis-

sues, taking about 48 hours for full effect. These quantitative chemical studies following large infusions of fat support previous tracer studies with radioactive-labeled fat, which indicated that heparin increases both the clearance of infused fat from the blood and the metabolic disposition of the fat in the tissues.

Acknowledgment

We are indebted to Mary Ann Skinner, William Vogel, and Vincent Hunt for skillful technical assistance.

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Hippocrates Aphorisms

The Father of Medicine, left posterity an invaluable heritage of observations and conclusions based on his personal experience and encapsulated in his immortal aphorisms. For example:

I. 20. When things are at the crisis; or when they have just passed it, neither move the bowels, nor make any innovation in the treatment, either as regards purgatives or any other such stimulants, but *let things alone.*

II. 2. When sleep puts an end to delirium, it is a good thing.

II. 39. Old people on the whole, have fewer complaints than young, but those chronic diseases which do befall them generally never leave them.

II. 44. Persons who are naturally very fat are apt to die earlier than those who are slender.

II. 54. Largeness of person in youth is noble and not unbecoming; but in old age it is inconvenient, and worse than a smaller stature.

V. 2. Spasm supervening on a wound is fatal.

Here we have evidence that the Greeks knew of lockjaw, or tetanus, the result of wound infection.

VII. 15. From a spitting of blood there is a spitting of pus.

Hippocrates was apparently well aware that sometimes a hemorrhage from the lung is the first sign of tuberculosis.

Fatal Neoplasms

1911-1962

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In 1953, Dr. E. T. Bell and I reviewed the experience of the Department of Pathology in the Medical School of the University of Minnesota with respect to fatal neoplasms for the years 1911-1952 inclusive. That study, summarized in part,[1] covered 12,004 deaths attributed to tumors in an overall material of 70,573 autopsies. Among the items of special interest provided by that survey were the results of the calculation of the proportions of deaths due to certain tumors in different periods of years. For example, the frequency of carcinoma of the lung in males for the period 1949-1952 inclusive represented a fourfold increase over the period 1911-1930 inclusive, while for females the rate was unaltered. There was a moderate decline in the frequency of gastric cancer after 1940. Carcinoma of the breast in females increased by two thirds in the period 1949-1952. As we were especially interested in what further changes might occur in subsequent years, it seemed worthwhile to review the experience of an additional decade. This paper combines the former data with that for the years 1953-1962 inclusive and now concerns 21,693 deaths attributed to neoplastic disease in 114,757 autopsies for the period 1911-1962 inclusive.

The autopsy records of the Department of Pathology represent a community-wide experience. For many years the Department provided direct autopsy service for the physicians of the community, for the coroner of Hennepin County, and, to a lesser extent, for the coroner of Ramsey County. Pathologists, employed in increasing numbers over the years by private hospitals, have continued to add their material to the collection. All of the public hospitals and nearly all of the private hospitals in the Twin City area are and long have been represented. As the result then of the generous help of many physicians in all areas of medical activity for a period now in excess of fifty years, a rich, broad-based material has been assembled.

Of importance in assessing the significance of the data derived from the autopsy experience is the proportion of deaths represented by that material. The numbers of autopsies have steadily increased over the years. In the earlier summary the ratio of autopsies to deaths in the Twin City area was calculated for the years 1949-1952 inclusive. The findings, reproduced in Table 1 show that the autopsies were equivalent to one third of the deaths among males and one quarter of the deaths among females. It has been estimated that similar proportions obtained back to 1930, while in earlier decades undetermined but considerably lower proportions were represented. During 1953-1962 the rate has risen. For this period of years the Vital Statistics summaries of the Minnesota Department of Health record the occurrence of 60,143 deaths for Hennepin and Ramsey Counties together. For this same period the available autopsy records total 22,963, a number equivalent to about 38 per cent of the deaths. Many factors, known and unknown, operate to bias the composition of autopsy material. Nothing short of complete coverage could approach the elimination of discrepancies between the real and the autopsy-encountered frequencies of diseases. It seems reasonable to believe, however, that our material, long representing about a third of the deaths in the community, provides an excellent sample of the lethal diseases encountered in that community.

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The total available autopsy material for the period 1911-1962 inclusive, subdivided into arbitrarily selected groups of years, is arranged, according to age and sex, in Tables 2 and 3. Together, the tabulations cover 114,757 autopsies (72,501 males, 42,256 females). Exclusive of stillbirths (3,190 males, 2,883 females) there are 108,684 autopsies (69,311 males, 39,373 females) representing all ages.

The proportions of acute deaths — accident, homicide, etc. — from the coroners' services have varied. Among males, such cases make up about fifteen per cent of the autopsies for the period 1911-1930, about six per cent for 1931-1940, about three per cent for 1941-1952, and again about six per cent for 1953-1962. Part of this study compares the incidences of various tumors in selected periods of time. Because the traumatic and related deaths furnish varying proportions of the total experience in the several periods, such cases have been omitted to provide a more homogeneous material within which to calculate the frequencies of deaths due to neoplastic disease, thus leaving 102,624 autopsies (64,441 males, 38,183 females) to form the basis for the tabulations. In the main the tables speak for themselves. Only a few comments will be added.

With reference to time, the over-all experience has been broken down to arbitrarily selected periods of years. The age distributions, expressed in per cent of the number of cases for each period, are provided in Table 4 for males and in Table 5 for females. For both sexes the great majority of the cases in the first decade are neonatal deaths. Beyond this decade there has been a decided shift in the age distributions in the several groups of years. For example, among males, deaths in the third decade amounted to 6.1 per cent of the total in 1911-1930 and 1.6 per cent of the total in 1958-1962. Deaths in the fourth decade provided 10.2 per cent and 3.8 per cent, respectively, of the same totals. By way of contrast, the eighth decade provided 9.1 per cent of the total in 1911-1930 and 21.3 per cent of the total in 1958-1962. Similar changes are exhibited in Table 5 for females. These findings reflect the aging of the population.

In 21,693 cases death was attributed to a tumor. The great majority are malignant. Benign tumors, lethal by virtue of position or other factors, are included. Tumors incidentally encountered at autopsy in patients dead of other causes, or tumors known to have been present, but not lethal, are excluded. In cases of multiple tumors only the tumor judged to be most responsible for death was counted. The deaths due to neoplastic disease, arranged according to frequency, age, and sex are summarized in Table 6 and comprise 13,589 (21.1 per cent) of 64,441 males and 8,104 (21.2 per cent) of 38,153 females. The frequencies range from a low of 3.5 per cent in the first decade to a high of 28.9 per cent in the seventh decade among males and from a low of 3.6 per cent in the first decade to a high of 33.6 per cent in the sixth decade among females. More than 85 per cent of the cases occur after age 40.

Table 7 shows, in numerical order, the neoplasms or groups of neoplasms responsible for the death of 13,589 males; Table 8 shows similar data for 8,104 females. Several points merit comment. There are undoubtedly errors in diagnosis, but these are believed to be rare insofar as the determination of kind of tumor is concerned. There are probably more frequent instances where the designation of the primary site has been a necessarily arbitrary and sometimes erroneous decision. This ever-present problem is reflected in the numbers of instances listed as "carcinomatosis, primary site undetermined." One cannot believe that the errors, while judged to be small in number, distribute themselves in such a fashion as to cancel out their effect on calculations based on the recorded totals. However, the broad pattern, at least for the frequently encountered cancers, should not be greatly affected.

The arrangement of some of the tumors in groups has been arbitrary and it is recognized that certain neoplasms have thereby lost identity. To list all varieties, however, seemed beyond the scope of this paper. For example, the sarcomas of all cell types and locations have been consolidated into one group which, it may be noted, is greatly outnumbered by the combined epithelial tumors. In general, the listed tumors follow familiar patterns with regard to frequency and sex differences. The age distributions of the ten most frequent tumors among males and females respectively are given in Tables 9 and 10. By way of contrast, attention may be invited to the impressively small proportion of the totals made up by carcinomas of the thyroid and major salivary glands.

As noted above, over 85 per cent of the deaths from neoplastic disease occur after age 40. Tables 11 and 12 give, for males and females over 40 respectively, the proportions of deaths caused by selected tumors as well as all tumors in successive periods of years. Throughout the entire study span of 51 years the incidences are generally stable. Three exceptions, however, seem noteworthy. Carcinoma of the lung in males shows the most striking change, with a rise from 1.04 per cent in 1911-1930 to 6.53 per cent in 1958-1962. On the other hand there is no material change in the rate for pulmonary carcinoma among females. For carcinoma of the stomach, formerly the most frequent fatal neoplasm among males, a gradual decline, first manifest in 1941-1944, has continued, the rate falling from about 5 per cent for the years 1911-1940 to 2.5 per cent for the period 1958-1962. Similar but less striking changes obtain for carcinoma of the stomach among females. Carcinoma of the breast among females showed a remarkably uniform incidence of about 3.3 per cent from 1911 through 1948. For the period 1949-1952 the frequency rose to above 5 per cent and has so continued through the decade 1953-1962. The general stability of the rates for the majority of the tumors listed through the entire period 1911-1962 serves to emphasize the changes which have occurred.

Summary

In an over-all material of 114,757 autopsies recorded in the Department of Pathology of the Medical School of the University of Minnesota for the years 1911-1962, inclusive, the deletion of acute traumatic and related deaths (because of varying frequencies in successive groups of years) and stillbirths leaves 102,624 autopsies on individuals of all ages. In 21,693 cases death was directly or indirectly the result of neoplastic disease (13,589, or 21.1 per cent, of 64,441 males and 8,104, or 21.2 per cent, of 38,153 females).

Over 85 per cent of the fatal tumors occurred past age 40. For this group the incidences for males and females respectively, of selected tumors as well as the incidences for all tumors within each of successive groups of years were calculated. For most tumors the rates remained stable, with three noteworthy exceptions. Carcinoma of the lung among males has shown a steady increase since 1940, and for the most recent period exhibits a rate representing a sixfold increase over that of 1911-1930. Carcinoma of the stomach in males has shown a gradual decline since 1940 to reach a level, for 1958-1962, which is half that of the earlier periods. A somewhat less pronounced fall obtains for females. The frequency of carcinoma of the breast among females increased by two-thirds in the period 1949-1952 and has since maintained the higher level.

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TABLE 1
Ratio of Autopsies to Deaths in Twin City Area for Years 1949-1952 Inclusive

Age	Males			Females		
	Deaths	Autopsies	Percent	Deaths	Autopsies	Percent
0-9	2075	1036	50	1483	672	45
10-19	223	124	56	136	76	56
20-29	364	236	65	262	136	52
30-39	591	320	54	518	184	35
40-49	1424	599	42	962	372	39
50-59	3533	1393	39	2008	568	28
60-69	5243	1695	32	3312	821	25
70-79	4891	1231	25	4235	794	19
80-89	2881	551	19	3284	388	12
90-100	434	51	12	688	40	6
Totals	21659	7236	33	16888	4051	24

TABLE 2
Males: Total Autopsies, 1911-1962 Inclusive

	1911-20	1921-30	1931-40	1941-44	1945-48	1949-52	1953-57	1958-62	Total
Stillbirths	44	603	964	225	139	234	453	528	3190
0-9	275	1233	1963	736	926	1036	1803	2071	10043
10-19	73	234	415	126	120	124	192	223	1507
20-29	197	432	736	182	225	236	294	365	2667
30-39	268	744	1168	333	346	320	483	654	4316
40-49	330	1003	2132	649	588	599	962	1235	7498
50-59	439	1114	2538	1130	1324	1393	1837	2141	11916
60-69	269	1282	2493	1151	1409	1695	3110	3549	14958
70-79	93	693	2001	998	1106	1231	2247	2997	11366
80-89	15	137	584	415	509	551	980	1125	4316
90-100	0	3	34	23	49	51	117	122	399
Age ?							135	190	325
0-100	1959	6875	14064	5743	6602	7236	12160	14672	69311
Total	2003	7478	15028	5968	6741	7470	12613	15200	72501

TABLE 3
Females: Total Autopsies 1911-1962, Inclusive

	1911-20	1921-30	1931-40	1941-44	1945-48	1949-52	1953-57	1958-62	Total
Stillbirth	33	489	791	236	128	219	491	496	2883
0-9	211	943	1411	514	620	672	1201	1373	6945
10-19	53	212	379	106	95	76	122	160	1203
20-29	147	439	690	189	179	136	169	196	2145
30-39	110	468	832	278	237	184	305	354	2768
40-49	115	495	1026	397	347	372	529	658	3939
50-59	111	519	1155	467	586	568	903	996	5305
60-69	78	476	1190	570	661	821	1412	1540	6748
70-79	29	245	1015	557	714	794	1415	1808	6577
80-89	7	77	300	255	342	388	863	981	3213
90-100	0	9	26	20	36	40	123	138	392
Age ?							51	87	138
0-100	861	3883	8024	3353	3817	4051	7093	8291	39373
Total	894	4372	8815	3589	3945	4270	7584	8787	42256

TABLE 4
Males: Distribution of Autopsies by Age in the Several Periods

Period	1911-30	1931-40	1941-44	1945-48	1949-52	1953-57	1958-62
No. Autopsies	7543	13127	5458	6361	7003	11376	13573
Age	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0-9	19.1	14.7	13.3	14.4	14.7	15.4	14.7
10-19	3.3	2.8	1.9	1.5	1.4	1.0	.9
20-29	6.1	4.6	2.9	2.9	2.7	1.7	1.6
30-39	10.2	8.0	5.5	5.0	4.2	3.5	3.8
40-49	14.7	15.0	10.9	8.8	8.2	7.5	8.0
50-59	17.6	18.0	19.7	20.1	19.4	15.3	14.7
60-69	18.1	17.9	20.1	21.5	23.6	26.1	25.1
70-79	9.1	14.5	17.8	17.1	17.2	19.1	21.3
80-89	1.7	4.2	7.4	7.9	7.8	8.4	8.0
90-100	0.3	0.3	0.4	0.8	0.7	1.0	.9
Age ?						1.0	1.0

TABLE 5
Females: Distribution of Autopsies by Age in the Several Periods

Period	1911-30	1931-40	1941-44	1945-48	1949-52	1953-57	1958-62
No. Autopsies	4444	7827	3285	3774	4051	6866	7936
Age	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0-9	25.5	17.9	15.5	16.2	16.6	16.9	16.7
10-19	5.3	4.7	3.0	2.4	1.9	1.5	1.5
20-29	11.8	8.5	5.4	4.6	3.3	2.2	2.0
30-39	11.9	10.3	8.1	6.1	4.5	4.2	4.1
40-49	12.9	12.8	11.8	9.1	9.2	7.3	7.8
50-59	13.1	14.4	13.9	15.2	14.0	12.8	12.0
60-69	11.7	14.8	17.1	17.4	20.2	20.0	18.8
70-79	5.7	12.6	16.7	18.9	19.6	20.3	22.3
80-89	1.8	4.0	7.7	9.0	9.5	12.5	12.1
90-100	0.2	0.3	0.6	0.9	1.0	1.8	1.7
Age ?						.5	1.0

TABLE 6
Incidence of Deaths Due to Neoplastic Disease with Respect to Age and Sex

	Males			Females		
Age	Autopsies	Tumors	Percent	Autopsies	Tumors	Percent
0-9	9776	339	3.5	6821	248	3.6
10-19	1152	190	16.5	1092	158	14.5
20-29	2012	363	18.0	1980	197	9.9
30-39	3651	586	16.1	2623	542	20.7
40-49	6746	1280	17.5	3798	1093	28.8
50-59	11139	2728	24.5	5144	1730	33.6
60-69	14196	4113	28.9	6582	1927	29.3
70-79	10928	2955	27.0	6456	1570	24.3
80-89	4175	938	22.5	3182	553	17.4
90-100	391	62	15.8	386	57	14.8
Age ?	275	35	12.7	119	29	24.4
Total	64441	13589	21.1	38153	8104	21.2

TABLE 7
Males: Fatal Neoplasms in Order of Frequency

Carcinoma of lung	1930
Carcinoma of stomach	1775
Carcinoma of colon and rectum	1664
Carcinoma of prostate	1071
All leukemias	1045
Carcinoma of pancreas	784
Hodgkin's disease and lymphosarcoma	757
Glioma	708
Carcinoma of bladder	504
Carcinoma of esophagus	448
Renal tumors	429
Carcinoma of mouth, nose and pharynx	401
Carcinoma of gallbladder and bile ducts	270
Carcinomatosis, primary?	219
Multiple myeloma	177
Carcinoma of liver	175
Malignant melanoma	134
Carcinoma of larynx	122
Carcinoma of skin (including lower lip, penis, anus)	115
Tumors of testis	98
Meningioma	90
Miscellaneous intracranial tumors	68
Carcinoma of thyroid	57
Carcinoma of small bowel	48
Tumors of hypophysis	37
Tumors of adrenal	26
Carcinoma of breast	15
Tumors of major salivary glands	11
Miscellaneous tumors and various sarcomas	411
Total	13589

TABLE 8
Females: Fatal Neoplasms in Order of Frequency

Carcinoma of breast	1231
Carcinoma of colon and rectum	1028
Carcinoma of uterus	773
Carcinoma of stomach	607
All leukemias	570
Carcinoma of ovary	532
Hodgkin's disease and lymphosarcoma	465
Glioma	414
Carcinoma of pancreas	351
Carcinoma of gallbladder and bile ducts	317
Carcinoma of lung	251
Carcinomatosis, primary?	181
Renal tumors	175
Carcinoma of urinary bladder	146
Meningioma	102
Multiple myeloma	88
Malignant melanoma	79
Carcinoma of esophagus	74
Carcinoma of liver	68
Carcinoma of mouth, nose and pharynx	65
Carcinoma of skin (including vulva and anus)	56
Carcinoma of thyroid	55
Miscellaneous intracranial tumors	32
Carcinoma of small bowel	23
Tumors of hypophysis	21
Tumors of adrenal	18
Carcinoma of larynx	5
Tumors of major salivary glands	3
Miscellaneous tumors and various sarcomas	374
Total	8104

TABLE 9
Males: Age Distribution of Leading Fatal Neoplasms

Age	Carcinoma of Lung	Carcinoma of Stomach	Carcinoma of Colon and Rectum	Carcinoma of Prostate	Leukemia	Carcinoma of Pancreas	Hodgkin's and Lymphosarcoma	Glioma	Carcinoma of Urinary Bladder	Carcinoma of Esophagus
0-9	0	0	0	0	143	0	15	76	0	0
10-19	0	0	2	0	63	0	22	50	0	0
20-29	3	5	18	0	80	2	85	53	1	0
30-39	60	42	53	0	74	19	74	86	4	1
40-49	214	170	143	12	104	67	97	118	24	32
50-59	540	365	306	95	177	155	153	152	80	121
60-69	746	580	510	314	217	271	175	123	170	156
70-79	308	462	437	415	137	211	109	40	161	107
80-89	51	131	178	216	41	51	24	8	58	27
90-100	2	13	8	14	5	1	1	1	4	2
Age ?	6	7	9	5	4	7	2	1	2	2
Total	1930	1775	1664	1071	1045	784	757	708	504	448

TABLE 10

Females: Age Distribution of Leading Fatal Neoplasms

Age	Carcinoma of Breast	Carcinoma of Colon and Rectum	Carcinoma of Uterus	Carcinoma of Stomach	Leukemia	Carcinoma of Ovary	Hodgkin's and Lympho-sarcoma	Glioma	Carcinoma of Pancreas	Carcinoma of Gallbladder & Bile Ducts
0-9	0	0	0	0	91	2	13	56	0	0
10-19	1	3	0	2	43	3	22	39	0	0
20-29	10	13	17	2	29	6	28	38	2	0
30-39	94	37	91	35	51	34	39	57	4	2
40-49	241	107	151	61	68	106	59	59	24	15
50-59	344	198	195	91	79	151	76	79	85	49
60-69	267	293	194	160	90	130	114	59	89	85
70-79	211	254	90	172	93	82	83	23	101	109
80-89	51	104	31	77	31	18	26	3	37	50
90-100	7	14	1	6	1	0	4	0	7	4
Age ?	0	5	3	1	1	0	1	1	2	3
Total	1231	1028	773	607	570	532	465	414	351	317

TABLE 11

Males Over Age 40

Incidence of Selected Fatal Neoplasms in the Several Periods of Years

Period	1911-30	1931-40	1941-44	1945-48	1949-52	1953-57	1958-62
No. Autopsies	4616	9180	4168	4846	5388	8914	10726
Carcinoma of:	0/0	0/0	0/0	0/0	0/0	0/0	0/0
Stomach	5.02	4.87	3.69	3.65	3.53	2.88	2.50
Colon	1.91	3.16	3.36	3.61	3.41	3.54	3.72
Lung	1.04	1.32	2.18	3.53	4.45	5.54	6.53
Prostate	1.82	2.19	2.69	2.33	2.66	2.11	2.13
Pancreas	1.32	1.10	1.27	1.55	2.08	1.73	1.90
Kidney	0.82	.53	.67	.97	1.08	.87	.91
Urinary Bladder	.82	.94	1.20	.99	1.15	1.14	1.05
Esophagus	.95	.65	.98	1.13	1.06	.86	1.05
Other tumors	5.47	6.77	7.13	9.81	6.72	8.46	9.22
Total tumors	19.17	21.53	23.17	27.57	28.14	27.13	29.01

TABLE 12

Females Over Age 40

Incidence of Selected Fatal Neoplasms in the Several Periods of Years

Period	1911-30	1931-40	1941-44	1945-48	1949-52	1953-57	1958-62
No. Autopsies	2021	4712	2231	2669	2944	5161	6012
Carcinoma of:	0/0	0/0	0/0	0/0	0/0	0/0	0/0
Stomach	3.06	2.31	2.55	2.29	2.72	1.80	1.76
Colon & Rectum	2.52	3.58	3.85	3.93	3.60	3.89	4.26
Lung	1.13	0.74	0.94	0.60	0.81	.89	1.19
Pancreas	1.53	1.02	1.39	1.48	1.26	1.36	1.41
Gallbl. & Ducts	1.08	1.53	1.12	1.27	1.49	.91	1.16
Breast	3.21	3.40	3.36	3.33	5.13	5.23	5.29
Uterus	3.46	2.93	2.69	2.81	2.31	2.27	2.26
Ovary	1.78	1.87	2.02	2.10	1.49	1.82	2.08
All others	7.27	6.69	7.67	8.02	10.43	9.51	9.31
Total tumors	25.04	24.07	25.59	25.85	29.24	27.68	28.72

Pulmonary Resection for

THE APPEARANCE of pulmonary metastases following resection of a malignant tumor was long considered an incurable condition. When Divis in 1926 and Torak in 1930 performed the first successful resections of metastatic lung tumors, there appeared to be hope for some of these patients. Interest was further stimulated in 1939 when Barney and Churchill[1] reported a five-year survival following pulmonary resection for metastatic adenocarcinoma of the kidney. This patient, who survived 23 years, remains the longest known survivor among cases of this nature.

Since then, many individual cases and a number of small series have been reported. In 1963 Oschner[2] found 500 cases reported. Most series of highly selected cases have recorded a definite salvage. Gliedman[3] in 1957 reported 29 patients from the University of Minnesota Hospitals; two from a possible nine had lived five years. In 1960 Moersch and Clagett[4] found that 30% of 73 patients undergoing pulmonary resection for metastatic malignancy had survived five years or more.

Clinical Findings

During the interval from June, 1949, to January, 1963, 30 patients were explored for metastatic lung disease at the Minneapolis Veterans Hospital. Ages ranged from 21 to 71 years, with a median age of 58 years. Twenty-three of these patients were found to have resectable lesions at the time of surgery. There were two operative deaths. One unresectable patient died at surgery as a result of a perforation of the right atrium; the other was successfully resected but died eleven days postoperatively of a massive pulmonary embolus.

A total of 25 procedures were performed upon the 23 patients that were resectable. Two patients had two separate thoracotomies. The frequency of the various types of procedures are listed in Table 1.

TABLE I
Type of Operation (23 patients)

Wedge	10
Lobectomy	9
Segmental	4
Pneumonectomy	2
Total	25

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*Department of Surgery, Minneapolis Veterans Hospital and the University of Minnesota.

HUGH A. MUZZALL, M.D.*
EDWARD W. HUMPHREY, M.D.*
Minneapolis, Minnesota

Metastatic Cancer

TABLE 2

Primary Lesion	Interval between Primary Operation and Pulmonary Resection (Months)	Survival since Pulmonary Resection (Months)
Osteogenic sarcoma of tibia	10	167+
Osteogenic sarcoma of femur	16	86+
Fibrosarcoma of groin	52	64+
Lymphangiosarcoma of pelvis	17	31
Myxosarcoma of thigh	11	5
Carcinoma of rectum	43	147+
Carcinoma of rectum	69	3
Carcinoma of rectosigmoid	30	13+
Carcinoma of colon	28	65
Carcinoma of rectum	44	20
Carcinoma of sigmoid	75	11 days
Carcinoma of cervix	31	96+
Cylindroma of larynx	15	14+
Malignant melanoma of foot	165	38
Malignant melanoma of back	15	7
Malignant melanoma of chest wall	21	9
Malignant melanoma of scalp	1	4
Carcinoma of kidney	190	21
Carcinoma of kidney	0	25
Carcinoma of kidney	0	66+
Carcinoma of kidney	23	24
Carcinoma of kidney	16	18
Carcinoma of kidney	40	14+

Patients marked + are still living.

The Five Year Survivals

It may be seen from Table 2 that seven patients survived five or more years following pulmonary resection. One patient died of metastases five years and five months after resection of two metastases from a colon carcinoma. The remaining six patients were all free of malignant disease when last seen. Two of the five-year survivors in the sarcoma group had osteogenic sarcoma of the lower leg. One has lived 14 years, the longest survival of the entire series, and the other, seven years. The third sarcoma patient had a fibrosarcoma of the groin and has survived five years and four months.

Two patients with carcinoma of the colon or rectum, one with adenocarcinoma of the kidney, and one with carcinoma of the cervix, have also survived over five years. In addition to this group, there are three patients who are at present free of disease, but have survived for periods of less than five years from the time of thoracotomy.

Of unusual interest is one patient who underwent surgery for adenocarcinoma of the submaxillary gland in 1942 and was found to have unresectable pulmonary metastases at thoracotomy in 1954. This man was still alive in February, 1963, 21 years later, despite widespread metastases.

Of the 12 patients known to have died, 10 had metastases at autopsy; and two with obvious clinical evidence of metastases died without a post-mortem examination. Three additional patients were lost to follow-up, but all had metastases when last seen. It is important to point out that the presence of more than one pulmonary metastasis does not automatically indicate a hopeless situation. Fifteen of the total group of 30 patients, nine of the 23 resected cases, and two of the seven five-year survivors had more than one pulmonary metastasis at surgery.

Discussion

One can observe from this series of patients, as well as from others in the literature, that there are individual cases with excellent results. Carcinoma of the rectum and osteogenic sarcoma have been especially encouraging. Although we have only one case of carcinoma of the cervix in this series, our result would agree with the generally good reports of others.

Indications for Resection

Since it is apparent that certain selected patients may be cured of a malignancy even after the onset of pulmonary metastasis, it is important to emphasize to each patient the necessity of frequent examination following surgery for cancer. It is the practice at this hospital to recall such patients for examination every three months for the first year after surgery, every six months for five years, and once a year thereafter. If a solitary pulmonary metastasis is found at any time, the patient is then evaluated for a possible resection of that metastasis. In addition to being an acceptable operative risk, the indications that we have used for this procedure are:

1. A tumor whose characteristic growth pattern offers some hope of finding a solitary metastasis. For example, this procedure would not be performed on a patient with a metastasis from a bronchogenic carcinoma.
2. Either solitary pulmonary metastasis or metastasis localized to one lobe of the lung.
3. Control of the primary lesion.
4. No other apparent metastasis. On occasion this has necessitated a preliminary exploratory laparotomy.

In this series, the interval between the surgery for the primary lesion and the subsequent pulmonary resection does not bear the same positive correlation to survival that others[2,4,5] have reported. Although it would be reasonable to assume that a slowly growing tumor that presents a pulmonary metastasis after a long period of time would give a greater chance for cure than a more rapidly growing tumor, this presupposes that there is a correlation between the rate of growth of a tumor and the number of metastases, a relationship which is not always true.

Extent of Resection

It has been our policy to perform a limited resection, conserving as much respiratory function as possible. Twenty-three of 25 procedures were a lobectomy or less. Only two patients in this group had a pneumonectomy. Since neither of these patients survived more than 18 months, it would suggest that a patient requiring pneumonectomy to remove all of the disease is not, as a rule, curable.

Summary

The results of pulmonary resection for metastatic cancer in 23 patients at the Minneapolis Veterans Hospital have been presented. Seven patients have survived for five or more years. Although the series is small, this survival is encouraging and reconfirms the fact that pulmonary metastases, even when multiple, do not necesarily denote an incurable condition.

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Pliny's* Treatment for Swelling of the Parotid Gland

"Bears' grease, mixed with equal proportions of wax and bull-suet, is a cure for imposthumes of the parotid glands; some persons add *hypocisthis*** to the composition, or else content themselves with employing butter only, after first fomenting the parts affected with a decoction of *fenugreek,*† the good effects of which are augmented by *strychnos*. She-goats' urine, made warm, is used as an injection for the ears; and a liniment is made of the dung of those animals, in combination with axle grease."

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*See Minnesota Medicine June, 1964, Page 716.
**An astringent extract from a plant.
†An Asiatic herb with aromatic seeds.

Just for Today

I will try to strengthen my mind, I will study, I will learn something useful, I will not be a loafer; I will read something that requires effort, thought, and concentration.— Flying High, August 1964

Therapy

Refuse to be ill. Never tell people you are ill; never own it to yourself. Illness is one of those things which a man should resist on principle at the onset.

— E. G. Bulwer-Lytton

Man knows his age; woman computes hers.— P. T. Barnum

The Attitude of the Ancient Church Toward Medicine

Part I

As history so tragically reveals, the reaching of some significant new high point in the growth of the human mind and spirit by a great leader is followed by confused regression on the part of his adherents. Jesus repudiated the regnant attitude which saw disease as divine judgment upon sin. The ill person was not a pariah to be rejected until he recovered or death overtook him.

Psychotherapy

Jesus saw his ministry as that of coming "to seek and to save the lost" (Luke 19:10). He did not conceive of human "lostness" merely in religious, otherworldly terms; he saw man as a whole in which the physical and spiritual needs are integrated. When he spoke of the coming of human renewal in the Kingdom of God, he saw it expressed in a variety of ways: "the blind receive their sight and the lame walk, lepers are cleansed and the deaf hear, and the dead are raised up, and the poor have good news preached to them" (Matthew 11:5). Viewed on historical grounds, his healing miracles seem to have been based on his unique ability to bring about spiritual and emotional transformations, providing the basis for the reversal of long-standing disease processes.

The Use of Drugs

There is little mention of his using any MATERIA MEDICA save in the account of the healing of a blind man in John 9:6-7 (Mark 8:23-24). Yet this did not imply a rejection of medical means. The attitude of the early Church was one of tolerance for all methods of healing. In the parable of the good Samaritan, Jesus mentions his use of wine and oil, commonly accepted as antiseptics and emollients in the ancient world, in treating the wounds of the man beaten by robbers (Luke 10:34). Paul advised Timothy to treat his flatulence with small doses of alcohol in the form of wine (I Timothy 5:23). The early Church numbered physicians in its ranks of whom the most famous was Luke. Though these physicians were often scorned in the ancient pagan world,[1] they found acceptance in Christianity.

Radical Asceticism

As the Church grew in affluence and influence in the late Roman Empire, it was caught in a tragic retreat from the high point represented by Jesus and the early Church. The doctrine of God's omnipresence underwent a change in meaning. A sense of fatalism afflicted the spirits of men within Christendom as they contemplated the disease, squalor, suffering and death about them. Faith had not conquered this fatalism but simply provided a new rationale for it. The only hope for salvation was in a heavenly realm. All reality was seen as divided between flesh or matter, inherently evil, and spirit or mind, inherently good. Because man was a physical being, subject to passions and appetites, he was bound to suffer. Human sexuality was despised; virginity was elevated as the supreme ideal. Illness was not to be triumphantly overcome but meekly accepted. Final redemption and the vision of God awaited release from the bonds of fleshly existence. — To be continued in November issue.

DONALD G. DAWE, Th.D.
St. Paul, Minnesota

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Editorials

Elexious Thompson Bell, M.D.*

1880-1963

ELEXIOUS THOMPSON BELL was born in Hatch, Mo, Aug 30, 1880. After high school in Monroe City, Mo, he entered the University of Missouri where he received the BS degree in 1901 and the MD degree in 1903. In the Department of Anatomy at Missouri, he was an assistant instructor 1902-1903, an instructor 1903-1907, and an assistant professor 1907-1910. He spent the year 1905-1906 in Germany at the University of Bonn. In 1910 he became an assistant professor in the Department of Anatomy of the Medical School of the University of Minnesota. In 1911 he transferred to the Department of Pathology. Here he was an assistant professor 1911-1916, an associate professor 1917-1920, became a professor in 1920, and was appointed head of the Department in 1921. This post he held until retirement age was reached in 1949.

Throughout his long career Dr. Bell was a stimulating, effective teacher and productive investigator. The correlation of clinical and pathological findings was foremost in his approach, and he was at his best in the conduct of autopsy and clinicopathological conferences. Many physicians vividly recall the

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*Arch Path, 77, 228, 1964.

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lively, informative discussions which marked these weekly exercises for many years. Retirement did not bring an end to his activity. For an additional decade he continued his research and, as a consultant, participated in and made a major contribution to the teaching program at the Minneapolis Veterans Hospital.

Among his publications which number near a hundred, Dr. Bell is best known for the long series of contributions dealing with diseases of the kidney, particularly glomerulonephritis. A monograph *Renal Diseases* was published in 1946 and revised in 1950. His concise and authoritative *Textbook of Pathology*, which reflected his own experience in large measure, appeared in eight editions from 1930 to 1956. Studies in more recent years dealt largely with diabetes and concerned both the changes in the pancreas and the vascular and renal complications of the disease. This work, much of which was carried on after retirement, was summarized in a monograph, *Diabetes Mellitus, a Clinical and Pathological Study of 2,529 Cases*, published in 1960.

Dr. Bell was a member of both local and national professional groups. For many years he was the driving force for and secretary of the Minnesota Pathological Society, the membership of which represented all branches of medicine. He was a member of the American Association of Pathologists and Bacteriologists and the American Association for Cancer Research and served as president of these organizations in 1933 and 1934 respectively. Among other honors, he received the Distinguished Service Award of the Minnesota State Medical Association in 1949, the American Cancer Society Medal in 1951, and the Banting Distinguished Service Medal of the American Diabetes Association in 1959. He was granted an honorary DSc by the University of Missouri in 1959.

These events and achievements are the outward and admittedly important landmarks of a rich, scholarly career. But alone they fall far short of providing an adequate expression of the full character of the man and the profound influence for good which he had on those around him and throughout the medical community. Dr. Bell was straightforward, unassuming, kindly, and tolerant. He had an uncommonly fine sense of humor. These attributes, coupled with great breadth of knowledge, wide interests, and an unsurpassed capacity for logical approach to a problem made him one whose opinion was highly valued and frequently invited. His door was never closed, and, without ceremony, he was always available to those who sought help with any matter, large or small. These are some of the more personal characteristic which, for Dr. Bell, captured and held the genuine admiration, respect, and affection of generations of medical students and of medical and nonmedical colleagues throughout his University, his community, and beyond. He was esteemed in perhaps an even more special way by the smaller group of men and women who had the high privilege of working as graduate students in his Department.

As the result of injuries sustained in an automobile accident which occurred while en route to and near the area of his early Missouri home, Dr. Bell died on Sept 16, 1963.

Robert Hebbel, M.D.
Minneapolis, Minnesota

Bell Museum

EVEN BEFORE Dr. Elexious Thompson Bell retired from the University of Minnesota Medical School in 1949, his friends began to wonder what they could do to honor this remarkable man. Everyone agreed that he would be most pleased with a tribute that furthered knowledge in his field. Thus, the idea of the E. T. Bell Pathology Museum was born.

The fund to establish this museum was begun in 1947 and enjoyed rapid growth in

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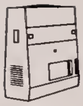

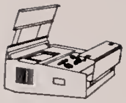

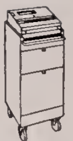

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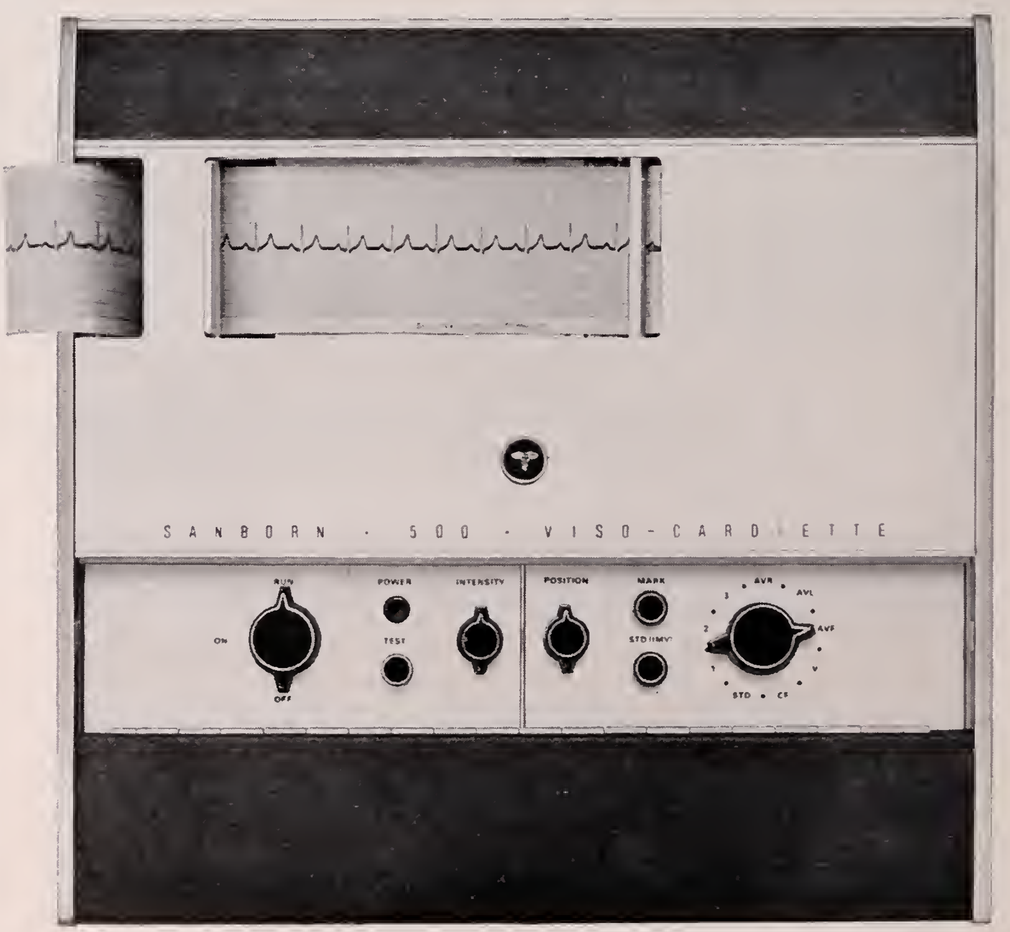

1949, when contributions poured in to mark Dr. Bell's retirement.

Originally, space was set aside in the area assigned to the Department of Pathology in the new Mayo Memorial building. However, in 1951, the plans for the building were revised, eliminating the two floors which were intended for the Department of Pathology and the pathological museum. Thoughts then turned toward including the museum in Diehl Hall. This also proved impossible. Finally, two years ago, space was allocated in Jackson Hall. Because of necessary remodeling, which is even now going on, this space is just becoming usable.

The museum is in the northwest corner of the ground floor of Jackson Hall, just beneath the small pathology class room. It encompasses approximately 1,500 square feet of space. This is a central location for students of medicine and physicians.

This will not be a conventional museum with large numbers of mounted gross specimens displayed in glass cases. Instead, it is designed to be a place where students and physicians can come to study the wealth of information which has been accumulated by the Department of Pathology. A vast amount of autopsy and surgical pathology material has been gathered, including autopsy protocols, microscopic sections, and color transparencies. Gross specimens supplemented by color transparencies will be available for study along with the protocols and the microscopic sections of all cases. A cross index will make all of these items easily accessible. To utilize these materials properly, small study cubicles need to be built and equipped with automatic projectors for viewing the color transparencies, and with microscopes for studying the sections.

Many members of the clinical departments are keenly interested in pathology and are continually asking to use the resources stored in the Department of Pathology. At present, this poses problems, since the specific items requested must first be located and collected, and then facilities provided for study. These difficulties will be overcome in the Bell Museum.

For second-year medical students, selected groups of color transparencies together with short descriptions will be placed in remote control projectors to enable students to study the materials at their convenience and at their own speed. The transparencies will illustrate the particular lesions which students are studying in their pathology courses. Many sets will have to be made up and changed as the courses progress.

Complete case histories, illustrating specific diseases and including brief summaries of the cases, laboratory findings, X rays, and other study aids such as autopsy reports with color transparencies of the gross and microscopic lesions will be set up. The histories, laboratory findings and X ray films will be copied on 35mm. color transparencies that can be projected for study. These permanent units are primarily intended for second-year students, but they may also be of use to other students and to physicians.

Of special interest to friends and former students of Dr. Bell is the section of the museum to be devoted to his memory. Here they will find early volumes of his books and permanent displays of the original plates made for them, along with some of the specimens he used in his research on diseases of the kidney. All of his texts will be displayed. Mrs. Bell has graciously consented to add some of his personal possessions. Dr. Bell's portrait, painted by Mr. Brewer, will be hung in this room.

Three rooms of the area are finished and ready to be furnished. Some of the items to go into them are already available and are scheduled to be moved soon, including microscopic sections, color transparencies, some gross specimens, and autopsy protocols.

One immediate need is for short-throw projectors and for microscopes for the study booths. Several will be purchased out of the interest the E. T. Bell Pathology Museum Fund has earned this year, so that the museum can begin serving students this fall. Eventually, at least a dozen projectors and microscopes should be purchased.

Although the finished portion of the museum is scheduled to open this fall without a curator, a full-time person will be a neces-

Continued

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sity when the rooms are in full operation. This person is needed to file and cross-index all of the materials and to make them available for study.

Building the color-transparency library, binding the autopsy protocols, purchasing slide projectors and microscopes, and furnishing the rooms calls for an initial investment of almost $17,000. All expenses must be paid by the E. T. Bell Pathology Fund which presently totals $70,325. Maintaining the museum with a full time curator should cost between $6,000 and $7,000 a year. No funds are available for this. An additional $200,000 is needed to insure continued support for the museum. Such a sum would earn interest sufficient to cover annual expenses including the salary of the curator. The E. T. Bell Pathology Museum committee is anxiously looking for interested individuals to help raise this money, so that the museum can become the dynamic teaching tool it was intended to be.

Although the fund has always been called the E. T. Bell Pathology Museum Fund, several people have asked whether the term museum is the proper designation for this area. The committee would appreciate your thoughts and suggestions. They would also enjoy having you visit the portion of the museum that will be in service this fall. It will be open during regular University hours.

Letter to the Editor:

This is just a line to congratulate you on the Editor's soliloquy in the August issue of Minnesota Medicine. I am sure this will be most pleasing to all who read it, and especially to those who testify in court from time to time. I hope that the State Medical Association will get back of this item, as many persons are suing for compensation when there is nothing wrong but aging; unfortunately, many of them are getting it. On a number of occasions I have brought this fact to the attention of referees of the Industrial Commission and to juries, but I rarely seem to have the ability to make the facts understood.

Nothing is more unfortunate than the fact that for each case there is always a physician who has testified that the conditions due to aging were attributable to occupation or injury. — J. A. Myers, M.D.

The Editor's Soliloquy

It is sometimes difficult to detect the true worth of a man who conceals his lack of knowledge by talking learnedly. Let us demonstrate our virtues, rather than just proclaim them. — C. O. R.

In all science error precedes the truth, and it is better it should go first than last.
—Horace Walpole

President's Letter Continued from Page 1175

dents, 7,300 graduates, 12,199 approved internships and 37,610 approved residencies.

There are, therefore, 49,809 approved training positions open for our graduates. In addition, there are many unlisted, unapproved and sub rosa traineeships available, as we well know. Suppose our graduating classes decided to utilize only the approved positions — each would spend more time in post graduate training than Dr. Bevan recommended for the entire medical course from high school to opening a practice. There are more residencies than there are medical students. And I often wonder whether today's intern spends as much time with patients as he does in conferences and teaching sessions.

The situation is the result of many factors. Every conceivable discipline is represented by a Specialty Board with the exception of General Practice which does not seem to have the courage to take the plunge. I have even heard rumors of a Specialty Board in Nuclear Medicine which is probably as restricted as the one established in 1949, originally known as the American Board of Proctology. Other responsible factors are the accelerated programs of the early 40's, federal grants, new hospitals, V. A.-University affiliations, pre-payment plans and the fetish of hospitals and individuals for recognition by almost any agency.

We may expect some important changes when the report of the Citizens Commission on Graduate Medical Education comes in. President John Millis of Western Reserve is chairman of this large and important group. It remains to be seen whether the report will eliminate or accentuate the present hodgepodge of graduate medical training, with the attendant town and gown struggle for supremacy of which most of us are aware. Let us hope that it will accomplish for graduate training results comparable to those of the Flexner report for medical school training. It may be that the work of the internship will be included in the medical school years and that graduate training will begin with the residency.

All of which is an oblique way of approaching the matter which I intended to write about in this letter. My paranoia over not being granted a degree upon graduation has long since dissipated itself — in 1936, the University of Chicago was the first school to drop the internship requirement for the M.D. Northwestern held out until 1949, and was the last. As far as I know, no graduate of any U.S. school can be granted a license to practice in any State at this time unless he holds the M.D. degree. Your State Board of Medical Examiners requires that an applicant for license must have had a year of post-doctoral training acceptable to the Board. If internships go out of style, as seems likely, the Board should be given credit for foresightedness.

J. P. Medelman M.D.

J. P. Medelman, M.D.
President
Minnesota State Medical Association

American Medical Writers' Association Citation

California Medicine receives the 1964 award of the American Medical Writers' Association as the leading state medical journal of the year. Appearing monthly, this journal presents meritorious scientific material that is original, timely, and of interest to all readers. The writing is literate, lucid, and unburdensome. The ratio of scientific communications to other material is commendably high. Presented in a clean, uncluttered format, California Medicine is a pleasure to the eye as well as a stimulus to the mind. Its strength lies in the fact that it patently reflects the progressive attitude of the medical profession of a great, forward-moving state.

Curbstone Consultation

Alcohol and Longevity

QUESTION: Are there any insurance statistics to indicate that the use of alcohol (in moderation) (in excess) decreases longevity?

ANSWER: We find in reference book "Selection of Risks" (which was published by the Society of Actuaries in 1957 and written by Pearce Shepherd and Andrew C. Webster) the following statistics:

A sub-division of the experience into eight classes gave the following results:

Intoxicated six times a year for day or evening only	277%
Intoxicated once a month for day or evening only	287%
Intoxicated once a week for day or evening only	328%
Intoxicated not oftener than three times a year, but lasting two or three days	332%
Intoxicated more than above	482%
Steady free user, no intoxication	183%
Has received treatment or cure for alcoholic habits	293%
Alcoholic habits not classified elsewhere	338%

The experience by age group at issue showed the relative mortality highest at the younger ages.

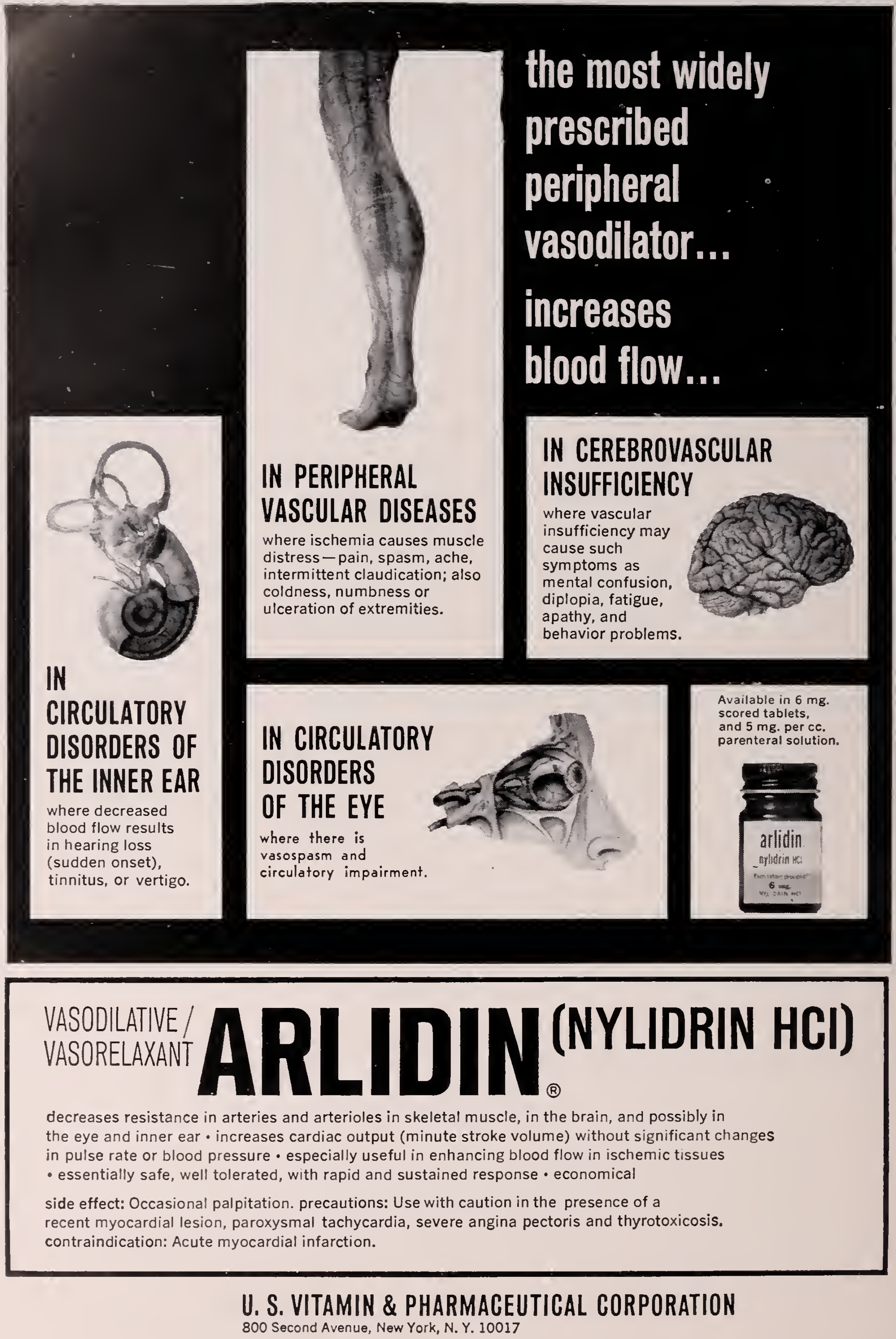
The social drinker generally will get a standard classification. Reformed drinkers show an improving mortality and the following table will give some indication of those where no treatment was required:

Last intoxication within two years of application	131%
Last intoxication between two and five years of application	134%
Last intoxication between five and ten years of application	107%
Last intoxication more than ten years prior to application	117%

There is evidence that total abstainers show more favorable mortality than nonabstainers.

In other words, the old adage that "He who drinks before forty is a fool, and he who doesn't drink after forty is also a fool" is not necessarily a good Chinese proverb statistically speaking. However, after the age of forty friendliness and fellowship surely is worth something even in the face of increased mortality.

Karl W. Anderson, M.D.
Vice President, Northwestern
National Life Insurance Company



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Fracture–Trauma Conference

Subcutaneous Cervical Emphysema

A patient who has incurred a wound of the neck and upon examination is found to have subcutaneous cervical emphysema presents a puzzling problem to the admitting physician. Where has the air come from and what should be done about it?

There may or may not be time for a deliberate and thorough examination before an emergency airway is needed. The offending agent has probably torn or perforated the apical pleura, trachea, larynx, or esophagus. The structure injured and the manner of treatment will determine the outcome of the case.

Case Reports

Case No. 1

An 18-year-old male was admitted to Hennepin County General Hospital on 12 June 1963 after the automobile in which he was driving struck another car and he was thrown against the steering wheel, striking his neck and head. Examination revealed a young man in acute respiratory distress thrashing about on the cart. He was intubated, but this did not seem to relieve his distress. His neck was swollen and crepitant. An emergency tracheotomy was then performed under local anesthesia. The trachea was found to be completely divided at the third ring beneath the cricoid cartilage, and as soon as a cuffed endotracheal tube was placed in the severed distal end the patient relaxed and breathed easily. It was deemed inadvisable to proceed with repair of the trachea at this time because of the head injury.

During the next few days his sensorium clared and on 17 June 1963 under general anesthesia an end-to-end repair of his trachea was performed using interrupted 2/0 chromic catgut sutures. A new tracheotomy was performed just proximal to the repair and below the cricoid cartilage. His wound healed per primum and his tracheotomy tube was removed on the twelfth postoperative day, but as the patient had not regained his preinjury mental status, a neurological consultant felt he had suffered cerebral damage secondary to hypoxia. He was transferred at this time to the care of his private physician.

Case No. 2

A 37-year-old male was admitted to Hennepin County General Hospital on 21 January 1962 with a bullet wound in the left side of his neck at about the level of the thyroid cartilage and adjacent to the anterior border of the sternocleidomastoid muscle. There was no wound of exit but an X ray revealed the bullet to be quite lateral and inferior in the right side of his neck. Subcutaneous emphysema was present, but there was no significant hematoma and no bleeding from the point of entry. After failure to visualize the perforation endoscopically and because of an increasing amount of subcutaneous air, a tracheotomy was performed under local anesthesia. He was started on large doses of antibiotics, and tetanus toxoid was given. His course was uneventful until the third post-injury day, when an induration was noted on the left side of the neck and there was an elevation of his temperature. On 26 January his temperature reached 104 degrees

Continued

and another endoscopic examination was made. This time a defect was noted in the posterior aspect of the upper esophagus with purulent drainage. He was taken to the operating room that afternoon, and through a generous incision along the anterior border of the sternocleidomastoid the left side of his neck was explored, and a retroesophageal abscess was drained. A gastrostomy was performed at this time.

His condition rapidly improved and the fistula closed spontaneously. His gastrostomy tube was removed and he was discharged on 11 February 1962.

In July of 1962 he was seen with a complaint of solid food sticking in his throat, and a barium swallow on X ray revealed an esophageal diverticulum at the point of old injury. He refused surgery at this time, but in March of 1963 with no improvement he submitted to an operation in which the diverticulum was excised. He has had no difficulty during the ensuing year.

Discussion

These cases illustrate certain points in the management of this condition.

The patient should have an upright chest X ray upon admission, to exclude a pneumothorax as the source for the subcutaneous air. If this should be the case, a posteroapical suction chest catheter placed, prior to any surgical procedure, will prevent further accumulation of subcutaneous air and correct the pneumothorax.

Should the patient not have a pneumothorax, it is quite likely that the trachea (more rarely, the larynx) or the esophagus is perforated. If an emergency tracheotomy has not been performed, as in Case # 1, there is good reason to perform one under local anesthesia prior to definitive surgery. Experience has shown that induction of anesthesia (particularly with pentothal) in patients with soft tissue wounds of the neck may trigger a laryngospasm with its attendant dangers.[1] An alternative method would be to cocainize the trachea and intubate the patient while he was still awake. One must also realize that positive pressure inhalation may exaggerate the air leak if the trachea is perforated below the tube or below the tracheotomy site.

The patient can then be moved to the operating room where a surgeon, familiar with complicated neck wound problems, can perform a careful exploration of the neck. Endoscopic examination of the upper esophagus after induction of anesthesia and before making the incision may reveal the site of perforation and simplify the surgery.

Wounds of the trachea and esophagus should be repaired primarily, and the latter drained. If an esophageal perforation has occurred, as in Case # 2, although no startling clinical signs are apparent, conservative treatment may result in an abscess, fistula, and the development of a diverticulum.

Summary

The presence of subcutaneous air associated with a neck wound indicates that formal surgical exploration is mandatory for optimum results. If a pneumothorax is present a suction chest catheter should be properly placed prior to surgery. Wounds of the esophagus and trachea require primary closure.

Harrison H. Farley, M.D.
Minneapolis, Minnesota

Reference

1. Lewis, R. S.: Wounds of the Neck and Larynx. Lancet (London) 1:781, 1944.

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Tumor Conference

Breast Papillomatosis

A 39-year-old mother of four children had nursed none of them because of nipple sensitivity due to a dermatitis and infection. The patient had milk secretion problems and soreness of breasts during pregnancies. Eight or nine years ago a biopsy of the left breast was declared to be cystic disease. The present lump is believed to have been present for over one year. The lesion is in the medial lower quadrant of the right breast, 4 cm. distal to the nipple and 1 by 1½ cm. in diameter. No palpable axillary nodes are found. The left breast is negative to palpation. No definite nodularity is present elsewhere. There is pain and discomfort of a mild degree which appears from time to time, unrelated to the menstrual cycle.

Excision biopsy was done by elliptical excision on December 10, 1963, and on frozen section was declared to be a papillomatosis. Several obvious small gross comedones caused some slight reservation about the possibility of comedo-carcinoma, since the gross appearance immediately after biopsy was at least compatible with comedo-carcinoma.

Final pathologic diagnosis: Benign papillomatosis and adenocystic disease (Figure 1 — see page 1254).

The Question or Problem

1. Is this condition premalignant?
2. Should a simple mastectomy be done for this condition and, if so, should it be bilateral?

Discussion

With reference to the literature, such authorities as Geschichter,[2] Haagenson,[3,4] and Ackerman[1] agree that the papilloma of the intraductal type is probably not premalignant, and that this patient likely has what is not a true intraductal papilloma, but a proliferative disease of an advanced degree, the result of multiple cystic disease, so-called Schimmelbusch's, which has never been demonstrated to be premalignant.

Figure 1 represents this case as compared to another case (Figure 2) of comedo-carcinoma with infiltrating intraductal carcinoma in a breast with associated cystic disease. However, this does not imply a causal relationship, even though the frequent finding of coincidental carcinoma with cystic disease sometimes presumes a relationship.

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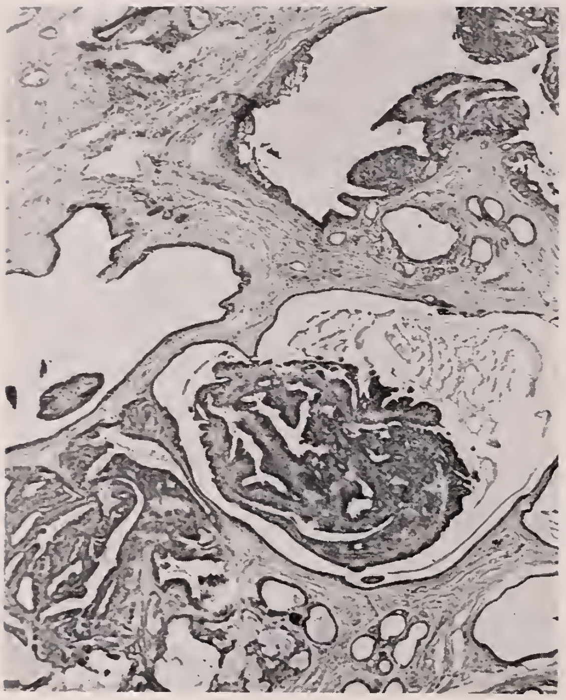

Fig. 1 — Breast papillomatosis — benign.

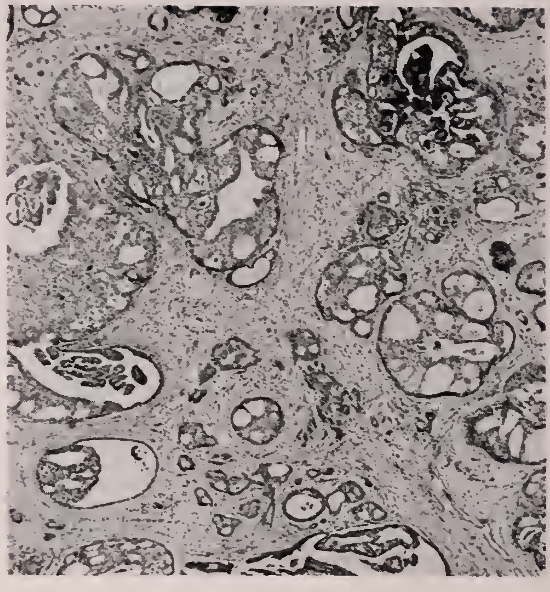

Fig. 2 — Comedo-carcinoma with infiltrating intraductal carcinoma and associated cystic disease — malignant.

Conclusions and Recommendations

Comedo-carcinoma can, at least in some instances, present a difficult problem upon decision by frozen section. Its gross appearance is quite different than that of scirrhous carcinoma but closely resembles cystic disease. The comedones represent heavy cellular growth of soft cells filling the ducts, similar to the debris in the dilated ducts of multiple cystic disease. The more cellular appearance of this debris or soft substance alerts the surgeon and pathologist to the possibility of comedo-carcinoma.

Results in this type of cancer are perhaps somewhat more favorable than the scirrhous carcinoma. Nonetheless, much better results in terms of cure are obtained by radical mastectomy.[2]

Since, in the case under consideration, carcinoma is eliminated, and since there is no evidence for the premalignant classification, no further procedure is recommended.

In case the patient should have frequent recurrence of lumps, a simple mastectomy or adenomammectomy, in which the breast tissue is shelled out, could be done to settle the problem of recurrent lumps, but it should not be done because of concern about possible impending malignancy.

J. H. Strickler, M.D.
Minneapolis, Minnesota

References

1. Ackerman: Surgical Pathology, III Ed. Mosby, St. Louis, 1964.
2. Geschichter, Chas., F.: Diseases of the Breast 2nd Ed. 1947 Lippincott. Philadelphia, pp. 207, 502.
3. Haagenson, C. D.: Papillary Neoplasms of the Breast. Ann Surg 133:18, 1951.
4. Haagenson, C. D.: Diseases of the Breast, W. B. Saunders Co., Philadelphia 1956 pp. 452, 156, 173.

Life is the art of drawing sufficient conclusions from insufficient premises.

— Samuel Butler

Clinical Path Conference

Complications Following Dilatation and Curettage

A 66-year-old white married female was admitted to the Gynecology Service on May 28, 1963, with the chief complaint of vaginal bleeding. Her menses had ceased at age 40 and she had had no vaginal bleeding until two months prior to admission. Menarche had occurred at age 14, with regular periods until the time of menopause. The patient had two children and had had two miscarriages. The past medical history indicated that a uterine suspension had been performed many years ago; she had had an appendectomy as a child; and several years prior to admission a cataract had been removed from the right eye. The rest of her previous medical history and family history was unremarkable.

Physical Finding

Physical examination revealed a well developed, well nourished white female. Blood pressure was 198/90 mm. Hg.; the pulse rate was 86 and regular. The lens of the right eye was absent. The chest was clear to auscultation and percussion. The aortic second sound was louder than the pulmonic sound. There was no cardiac enlargement and no murmurs were heard. The abdominal examination was negative. Pelvic examination showed atrophic vaginal mucosa. The cervix was observed to be atrophic with a serosanguineous fluid issuing from the cervix.

Laboratory Findings

Hemoglobin was 11.8 mg.%; the white blood cell count was 8800 with 86% neutrophils and 14% lymphocytes. Urinalysis was normal. A Papanicolaou smear was done on admission and reported to be highly suspicious for malignancy. On the basis of this test, a cervical conization was planned.

Progress

On the fourth hospital day the patient's temperature rose to 100.2° F. A urine specimen obtained by catheter showed greater than 100,000

Continued

colonies of a paracolobactrum organism sensitive to tetracycline, chloromycetin, gantrisin, and mandelamine. Therapy with tetracycline was begun on June 2, 1963, using a dosage of 500 mg. every six hours.

Operative Procedure

The patient rapidly became afebrile, and five days later on June 7, 1963, a cervical conization and a D & C were done. Postoperatively there were no apparent complications. A mild fever, up to 100.4° (oral), occurred on the first postoperative day. Two days later she was discharged. At this time the tetracycline was stopped, and she was given gantrisin 0.5 gm. to take four times daily for an additional five days at home. On the day of discharge, June 9, 1963, the nurses' notes contain the statement that the patient was complaining of some mild abdominal pain.

The pathologist reported that examination of the cervical cone specimen showed an early invasive carcinoma of the cervix. A letter was therefore sent to the patient requesting her to return to the hospital on June 14th for further therapy.

Readmission

At 3:00 A.M. on the morning of June 13, 1963, the patient was returned to the hospital via ambulance in critical condition and promptly admitted to the Medical Service. She appeared to be in a state of very severe shock and semicoma.

History

The history obtained from the patient's husband was very scanty. He reported that she had complained of lower abdominal pain, and had had vomiting and a watery diarrhea since returning home. The stools had occurred approximately every half hour since the time she was discharged from the hospital. On the night of her admission her moans had awakened the husband, who called the ambulance when he was unable to arouse her.

Physical Findings

Physical examination showed an unresponsive white female whose skin was very dry and pale. Blood pressure was unobtainable. The pulse was 120 and regular. The respiratory rate was 30 per minute. The temperature was 100.8° F (rectal). The mucous membranes of the mouth were noted to be very dry. The neck was supple, and the lungs and heart showed no abnormality. An electrocardiogram showed a sinus tachycardia. Abdominal examination gave no evidence of organomegaly. There were midline and right lower quadrant surgical scars. Bowel sounds were hypoactive; there was some increased muscle tone on the right side with mild distention and tympany, but no true rigidity or rebound tenderness. The patient moaned when the abdomen was palpated. Neurologic examination showed active deep tendon reflexes with no pathologic reflexes of the toe. The patient responded poorly to pain. Kernig's sign was negative. Pelvic examination showed dark, old blood in the vagina with a normal appearing postoperative cervix. There was fullness and tenderness in the right adnexa; but the left adnexa was thought to be normal. Rectal examination showed a large amount of loose, watery, white stool, which appeared purulent and gave a 3+ positive Guaiac reaction.

Laboratory Findings

The hemoglobin was 17.3 gm.%, and the white count was 17,700 with 58% neutrophils and 42% lymphocytes. The hematocrit was 54%. Urinalysis showed a specific gravity of 1.015 with a trace of albumin and 50 to 70 red cells per high power field. The blood sugar was 125 mg.%, CO2 combining power was 9.5 mEq/L, and chlorides were 99 mEq/L. At this time, possible diagnosis and further tests to be performed were discussed.

Discussion

Dr. Calvin Bandt*

This woman entered the hospital because of vaginal bleeding, and a cervical biopsy revealed an early carcinoma of the cervix. Four days after her discharge, and one day prior to her scheduled readmission for cancer therapy, she was brought to the hospital in the middle of the night with fever, circulatory collapse, and in semicoma. The scant history available reveals that she has had a rather remarkable diarrhea for four days. Physical examination shows dehydration and questionable evidence for an intra-abdominal process. Confirmation of the history of diarrhea is shown by white, watery, Guaiac positive stool present in the sigmoid colon. All of these sound as if this lady was taken by some acute choleriform illness.

Diabetic Coma

Some of the things that should be initially considered from the clinical story are diabetic coma, mesenteric artery occlusion, and intestinal obstruction. I am sure the admitting physician considered diabetes, as one of the initial laboratory tests done was a blood sugar. We find the CO2 combining power 9.5 mEq/L, and in a dehydrated, semicomatose patient this would fit well, except for the essentially normal blood sugar. I would think it impossible for a diabetic to be in coma and not have hyperglycemia or glycosuria.

Intestinal Obstruction

The abdominal findings are not really striking, but with abdominal pain and vomiting, intestinal obstruction should be considered. However, the distention is not marked; the bowel sounds were described as hypoactive; characteristic borborygmi are not described; and furthermore, diarrhea is generally not a feature of intestinal obstruction.

Mesenteric Artery Occlusion

Diarrhea may be seen with mesenteric artery occlusion; shock comes as a secondary feature with pooling of venous blood and the Gram-negative septicemia that follows bowel necrosis. However, constipation is more common, and when diarrhea does occur, it usually is bloody. In addition, pain is a most constant symptom, usually very severe and with violent onset. As far as we can determine, this lady did not exhibit these findings.

As one reads over the protocol, the time relations here seem to indicate that her present problems are a result of her previous hospital stay. A

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*Department of Internal Medicine.

Continued

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woman of this age could have some process arising seemingly *de novo,* but I would think it quite unlikely in this case.

Perforation of Uterus

Six days prior to the present admission, she had a dilatation and curettage of the uterus with conization of the cervix. Either or both of these are usually well tolerated, but as in any procedure, complications can occur. The most frequent complications of a dilatation and curettage with conization are bleeding or perforation of the uterus. There is no historical or objective evidence of the former, and the hemoglobin increased rather than decreased. Hemorrhage therefore seems quite unlikely. Perforation of the uterus, with an infection introduced simultaneously, would account for many of the abdominal findings. She was noted to have a fullness in the right adnexa, and there was an increased muscle tone on the right side, both of which could come from a pelvic abscess. Peritonitis cannot be excluded; she apparently does have an ileus. A late stage of peritonitis can be seen where the abdomen, beyond the stage of board-like rigidity, becomes softer to palpation. Associated with this, there could be a Gram-negative septicemia with endotoxin shock to account for her moribund state. Diarrhea does occur with Gram negative sepsis, but I doubt that it would be this severe and the stools would not be purulent. Here a more detailed history would be of value; but I get the impression that the shock symptoms appeared late, and were probably secondary to the diarrhea.

Cholera

If this lady were living in a country where sanitation was not well controlled, I am sure a prime consideration would be cholera, but under the present circumstances, I think it very unlikely. Salmonella and Shigella rarely produce this severe a degree of dysentery in adults, and there is nothing in the history to suggest exposure to or infection with these. I doubt if this diagnosis could be made on clinical grounds without the supporting evidence of a stool culture that would be positive for these organisms.

Staphylococcus

The only other bacterial organism that can produce a severe purulent gastroenteritis is the Staphylococcus. Such infections are characterized by fever, abdominal pain, severe diarrhea, abdominal distention due to ileus, and later shock. There are many names attached to this clinical and pathologic picture, and the most frequent synonym has been pseudomembranous enterocolitis. There has been some discussion in the literature as to whether this is the same as a true staphylococcus enteritis.

The Disease of Antibiotics

It has been called a disease of antibiotics, yet the first cases described as pseudomembranous enterocolitis were published in the 19th century, and many others were described before the advent of antibiotics. Most of these earlier cases followed surgical procedures on the abdomen or some other form of trauma, and it was postulated that shock was an etiological agent. These factors plus the observation that stool cultures of these patients were said to contain nonpathogenic organisms have led some observers to state that pseudomembranous enterocolitis is a distinct entity, with staphylococ-

Continued

cal enteritis only a variant. This may be true, but more recent case reports show a much higher incidence of positive cultures for the Staphylococci. It might also be pointed out that only recently have hospital laboratories used culture media that will favor the growth of Gram-positive organisms when culturing a stool or have considered the presence of Staphylococci in the stool of significance, and therefore reportable.

Pseudomembranous Enterocolitis vs Staphylococcal Enteritis

Whether or not pseudomembranous enterocolitis and staphylococcal enteritis are the same, it can be stated that a form of fulminating enteritis due to staphylococcus does occur. Its relationship to the use of antibiotics is very intriguing. A large percentage of the cases seen today do follow their use and almost all antibiotics including penicillin have been implicated. Most frequently this enteritis follows the use of broad spectrum antibiotics. It has occurred in cirrhotics following the use of neomycin to suppress intestinal bacterial growth; in surgical patients given antibiotics for a preoperative "sterilization" of the bowel; and even following streptomycin employed in the treatment of tuberculosis. It occurs following the use of parenteral antibiotics, as well, since many of them — especially the tetracyclines — are excreted in bile and thus enter the gastrointestinal tract. The mechanism favoring the development of pseudomembranous enterocolitis is believed to be an alteration of the flora in the intestine, which favors the growth of staphylococci in large numbers. A prerequisite to this is, of course, that staphylococci be resistant to the antibiotic employed. Since this is so frequently the case the more resistant organisms soon predominate. I shall return later to a little more thorough discussion of the relationship of the intestinal flora to the growth of the staphylococci.

The Exotoxin of Staphylococci

As for the cause of enteritis, it has been postulated that this is due more to the exotoxin produced by the staphylococci than to the actual infection of the organisms themselves. Prohaska[1] was able to produce the same clinical and pathologic picture in dogs fed the staphylococcal exotoxin as in animals fed antibiotics. Pathologically the small bowel of these animals shows edema of the submucosa with inflammation, necrosis, and ulceration of the mucosa. Prohaska also observed that the enteritis could not be produced unless the organisms normally residing in the bowel are destroyed. This seems to substantiate the older presumption that these organisms must be almost entirely abolished before the staphylococcal infection can take over. If true, this may explain why we do not see more staphylococcal enteritis than we do, considering the widespread use of antibotics. Apparently we must have the following situations occurring simultaneously: (1) a particular ecology in the large and small bowel in which the normal intestinal flora are suppressed, and (2) introduction of a staphylococcal organism capable of producing an exotoxin. In the occasional cases where no antibiotics have been used, one must hypothesize that surgical procedures on the abdomen, together with diet alterations and other unknown factors, have in some way alone altered the flora to such an extent that a superinfection with Staphylococci becomes possible.

Pseudomembranous Enterocolitis

With these thoughts in mind, our patient does become a candidate for staphylococcal enteritis. She did receive a broad spectrum antibiotic and apparently recovered from the disorder for which the antibiotic was given. However, on the seventh and final day of therapy, when she was to be discharged from the hospital, we note that the nurses record complaints of some abdominal pain. This was considered unimportant and the patient was allowed to go home. There she began to have this very voluminous diarrhea. The clinical picture upon admission is that of fever and shock. Presumably the shock in this case was due to the very large amount of fluid lost in the gut. In severe cases of staphylococcal enteritis this can approach 8-10 liters per 24 hours, approximately the same as is classically seen in Asatic cholera. When one considers that this fluid lost from the bowel contains in each liter approximately 100 mEq of sodium, 20 mEq of potassium, and 35 mEq of bicarbonate, it is easy to see why she would be in hypovolemic shock and metabolic acidosis. The rapid respiratory rate and rapid pulse would be consistent with this. The findings in the abdomen, indicating some degree of peritonitis, would not be inconsistent with this clinical picture. Pathologically, we would expect to see severe necrosis of the mucous membranes of the small and large bowel, with considerable inflammation of the bowel and visceral peritoneum. Enough irritation of the peritoneum could be present to account for the apparent swelling and tenderness reported on pelvic examination. The distention and tympany reflect a relative ileus found with this form of enteritis. Very frequently the large amounts of fluid that may be pocketed in the lumen of the bowel produce a radiologic appearance of intestinal obstruction. Fluid levels may be present if there is sufficient air. The neurologic picture of semicoma would be consistent with the long period of shock. The purulent, watery stool is a classical finding, and the 3+ positive Guaiac test reported could result from hemorrhagic necrosis that had occurred in the bowel wall. The hemoglobin was 17.3 gm.% on readmission; this compared with the previous hemoglobin of 11.8 gm.%, presumably reflects the marked dehydration that has occurred. The white count is not excessively elevated — only 17,700 with 58% neutrophils. If this were a classical Gram-positive sepsis, one would expect a much higher granulocyte count with a shift to the left. This latter is not stated, but I could presume that a toxic depression of the bone marrow associated with this degree of illness prevented a greater response. The urinalysis is remarkable only in that the specific gravity is 1.015. I would expect a much higher specific gravity in view of the severe dehydration that is present. Since the kidneys were unable to concentrate beyond this relatively low specific gravity in the face of severe water and electrolyte loss. I would suspect that there was also a renal abnormality. We know from her previous admission that she had a urinary tract infection, probably a pyelonephritis. We do not know if she had had previous bouts, and might possibly have a chronic pyelonephritis. Another possibility of kidney lesion would be renal tubular necrosis secondary to the staphylococcal enteritis, which could be due to the prolonged periods of shock and possibly to the toxin produced by the organism itself. Patients with staphylococcal enteritis frequently have severe tubular necrosis and complete renal shutdown. The fact that the serum chlorides level was

Continued

99 mEq/L is not disturbing; the fluid that is lost from the bowel in enteritis such as this is nearly isotonic with the body fluid as far as the chlorides are concerned. Since both water and chlorides would be lost at approximately the same rate, their levels would not be severely lowered, even though the total body stores were greatly depleted.

In summary then, I believe this lady has staphylococcal enterocolitis, and, as an associated factor, she probably has renal tubular necrosis.

Clinical Diagnoses:

1. Pseudomembranous enterocolitis
2. Pyelonephritis
3. Tubular nephrosis

Pathology

Dr. John I. Coe*

May I first congratulate Dr. Bandt on the excellence of his discussion and completely correct diagnosing of the pathological conditions present in this patient.

The Organism

The further test done to establish the diagnosis was a Gram stain on a smear of the stool. This showed a large number of Gram-positive cocci in pairs, clusters, and short chains. Cultures revealed these to be hemolytic Staphylococcus aureus, coagulase positive, and numerous colonies of gamma streptococci. There was no growth of Gram-negative organisms. The staphylococcus was later shown to be sensitive to oxacillin, methicillin, vancomycin, and oleandomycin and resistant to tetracycline, chloromycetin, penicillin, neomycin, and erythromycin.

The Treatment

The patient was treated with plasma, intravenous fluids, and vasopressors. Initial antibiotics were intravenous methicillin 6 gm. daily and vancomycin 2 gm. daily; in addition, intravenous hydrocortisone was given. Despite this she remained semicomatose. The blood pressure ranged between 80 and 100 mg. Hg. systolic. The urine output the first day was only 140 cc. even after 12.5 gm of mannitol were given intravenously in an attempt to stimulate an osmotic diuresis. In spite of the poor kidney function, vancomycin was continued because of her grave condition.

After hydration the hemoglobin fell to 12.5 gm./100 ml.; the white blood count rose to 86,700 with 92% neutrophiles exhibiting a marked shift to the left. Numerous histiocytes were present in the peripheral blood smear. Phagocytosed cocci were seen in some white blood cells. The blood urea nitrogen was 82 mg.%, serum sodium 128 mEq/L, and the prothrombin time was 30 seconds with a control of 11.8 seconds. The patient remained semicomatose, oliguric, and in shock. The temperature rose to 104° F (oral) and she expired early on the third hospital day.

Autopsy Findings

At autopsy there was bilateral pleural effusion with some pulmonary congestion and edema. The heart showed a mild myocardial fibrosis. The significant pathology was limited to the kidneys and gastrointestinal tract. The former were contracted with some irregular gross pits consistent with a chronic pyelonephritis. On section, the parenchyma was rather pale, but the corticomedullary junction was distinct. The ureters and bladder appeared normal. In the gastrointestinal tract, the esophagus, stomach, duodenum, and jejunum were all grossly normal.

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*Chief of Pathology, Hennepin County General Hospital.

Entera Colitis

Beginning at the jejuno-ileal junction and extending distally, the normal rugal pattern of the small intestine was lost, and what remained was a thin-walled dilated, smooth-surfaced tube filled with brownish, clear fluid. When the contents were emptied the mucosa appeared to be absent, and the lining that remained showed many small punctate hemorrhages. In the colon the mucosa appeared shaggy with numerous superficial ulcers. When the surface was wiped, fibrinous membrane was removed, again revealing numerous petechial hemorrhages in the underlying tissues. The wall did not appear thickened and the serosa throughout appeared normal.

Acute Tubular Nephrosis

Microscopically the kidneys showed areas of lymphocytic infiltration extending into the medulla, consistent with a chronic pyelonephritis. Besides this inflammatory change there was an acute tubular nephrosis manifest by hydropic change in some cells and in eosinophilic coagulation necrosis in others. Involvement of the proximal tubules seemed most prominent. Sections of the small intestine revealed the epithelial cells in the tips of the villous processes to be missing, while those in the crypts remained intact. There was an acute inflammatory reaction involving the mucosa and submucosa with little evidence of extension into the musculature (Fig. 1). At greater magnification, there was found to be edema, neutrophilic infiltration, and focal areas of acute hemorrhage. Many of the capillaries contained platelet and fibrin thrombi (Fig. 2). In a few areas clumps of Gram-positive cocci were found growing in the lamina propria (Fig. 3). Sections of the colon showed a more severe involvement, with

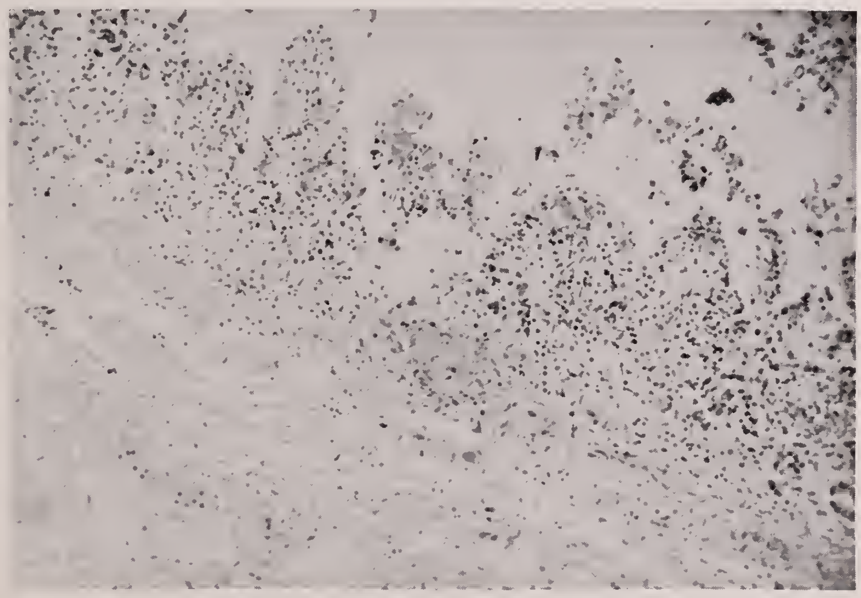

Fig. 1 — Photomicrograph of ileum (x30) showing inflammation and loss of superficial epithelial cells on villous processes.

Continued

many superficial ulcers extending into the submucosa and the presence of membrane composed of fibrin and necrotic debris. The histological appearance is considered to be that of a pseudomembranous enterocolitis as described by many previous investigators.

In the 16 years that we have kept coded autopsy diagnoses at the Hennepin County General Hospital, there have been nine cases of pseudomembranous enterocolitis. All of these have occurred in patients receiving broad spectrum antibiotics prior to the development of the disease, and all have had hemolytic coagulase positive Staphylococci as the principle organism obtained from stool cultures. There must be other factors, how-

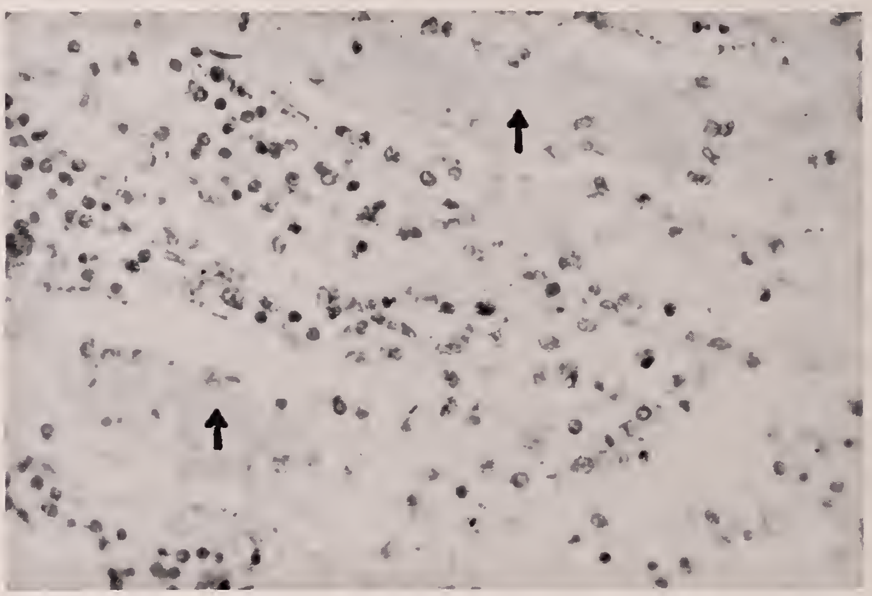

Fig. 2 — Photomicrograph of ileum (x400). Note edema, inflammation and fibrin thrombi in capillaries (arrows) of villous processes.

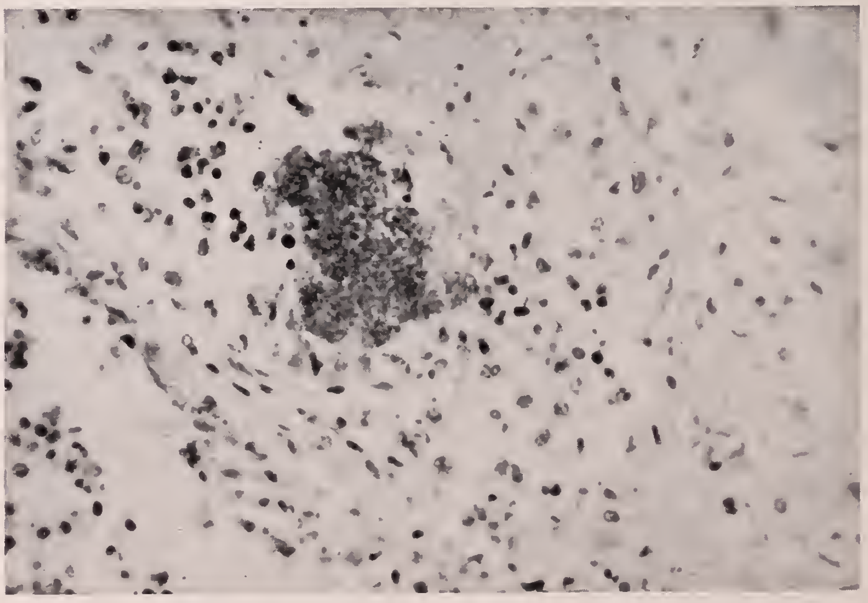

Fig. 3 — Photomicrograph of ileum (x400). A clump of Staphylococci are seen in the lamina propria.

ever, since in the same 16 years several patients at the hospital, following the use of broad spectrum antibiotics, have developed pure cultures of hemolytic coagulase positive Staphylococcus aureus on repeated tests of the stools, while manifesting no symptomatology of intestinal disease. However, no tests were made for the presence of enterotoxins, so that the symptomless course of these patients may have been due to the absence of any poison being produced.

Final Anatomic Diagnoses

1. Pseudomembranous staphylococcal enterocolitis.
2. Acute tubular nephrosis.
3. Chronic pyelonephritis.

Calvin Bandt, M.D.*
John I. Coe, M.D.**
Hennepin County General Hospital

Reference

1. Prohaska, J. V.: Role of Staphylococcal Exotoxins in the Induction of Experimental Ileitis. Ann Surg 118:492, 1963.

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*Department of Internal Medicine, Hennepin County General Hospital.
**Chief of Pathology, Hennepin County General Hospital.

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Advances

Bacteremia: Microbes, Manifestations, and Methods of Management

Part II — Gram-Negative Bacilli*

WILLIAM J. MARTIN, M.D.**
Rochester, Minnesota

Enterobacilliary Bacteremia

The incidence of bacteremia due to gram-negative bacilli of enteric origin appears to have increased progressively in recent years. In the fifteen-year period 1940 through 1954 at the Mayo Clinic, there were 137 cases of bacteremia due to gram-negative bacilli,[9] while in the five-year period 1955 through 1959, there were 113 cases.[10] In all, 303 cases of bacteremia due to gram-negative bacilli, excluding cases of endocarditis and typhoid fever, were observed at the Mayo Clinic in the period 1940 through June 1961.[11] These surveys included infections due to Pseudomonas organisms and those due to certain members of the family of Bacteroides which may have enteric residence but are not classified currently as Enterobacteriaceae. In this essay bacteremia due to these latter organisms will be considered separately. The increased number of cases of bacteremia due to gram-negative bacilli observed in recent years is disproportionate to the augmented number of patients seen.

Predisposing Factors

In about half of our cases, there was an apparent precipitating surgical or instrumental procedure. The underlying diseases, which were present in a significant percentage of cases, included advanced arteriosclerosis, 20 per cent; malignant disease, 10 per cent; hematologic disease, 15 per cent; diabetes mellitus, 10 per cent; and hepatic cirrhosis, 5 per cent. In addition to operation and manipulation, treatment capable of altering the defense mechanisms of the host had been used, including administration of adrenal cortical steroids in 15 per cent of the cases and antimetabolic agents in 5 per cent. Prior effects of certain forms of antimicrobial therapy, such as penicillin-induced suppression of the gram-positive elements of the bacterial flora, appeared to be a factor in the genesis of bacteremia in 20 per cent of the cases. Roentgen therapy had been given to less than 5 per cent of patients in whom bacteremia subsequently was diagnosed. In some cases these possibly predisposing or precipitating factors were multiple. Knowledge of predisposing factors and awareness of the possible supervention of bacteremia due to gram-negative enterobacilli in susceptible individuals facilitate early diagnosis and appropriate treatment.

Type of Enterobacillary Organism

Members of the coli-aerogenes group of organisms continue to be the most common cause of bacteremia due to gram-negative enterobacilli. Coli-aerogenes organisms cause about two thirds of these bacteremias with E. coli being responsible about twice as often as Aerobacter aerogenes. The remaining cases are most commonly due to Proteus organisms. Organisms less commonly responsible include Paracolobactrum, Klebsiella, Alcaligenes, Salmonella (excluding Sal. typhosa in this instance), and Shigella.

Treatment

Our practice has been to initiate antibiotic therapy empirically on clinical findings or on

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*See Part I, Minnesota Medicine September, 1964.

**Section of Medicine, Mayo Clinic and Mayo Foundation.

receipt of reports of blood cultures positive for gram-negative enterobacilli. If in vitro susceptibility tests later indicate the choice of treatment has been less than optimal, one reevaluates the program. Early in our experience, it became apparent that some of these patients were responding to a method of treatment which in vitro tests indicated would not be optimal. Since the patients were doing well, the treatment was continued unchanged. As yet the exact basis for this paradox has not been detected. Bacteremias due to A. aerogenes and Proteus organisms appear best to exemplify this "therapeutic paradox" that may be encountered in the management of infections of the bloodstream caused by gram-negative enteric bacilli, since in a significant number of our cases in vitro studies had indicated resistance of the organisms to tetracycline and streptomycin, yet combined treatment of patients with these antibiotics was followed by recovery.

Tetracycline

On receipt of reports of positive blood cultures, or after blood has been obtained for cultures in patients suspected of having bacteremia due to gram-negative enterobacilli, 500 to 750 mg. of a tetracycline is given by mouth every six hours if circulatory collapse appears not so severe as to prevent its intestinal absorption. Chloramphenicol may be given instead, orally in amounts of 0.5 to 1 gm. every four hours, if staphylococci also are present (furunculosis) or if superinfection with them seems especially likely. Again, chloramphenicol may be substituted if there has been inadequate response after about a 12 to 24-hour trial of tetracycline, or if in vitro data later indicate greater susceptibility to chloramphenicol and there has been poor response to the tetracycline.

Conjointly Given Antibiotics

Although streptomycin usually is given conjointly with the tetracycline, kanamycin may be substituted when a staphylococcal coinfection is possible, or either kanamycin or polymyxin B when response is inadequate. In addition to its effectiveness against Pseudomonas organisms, polymyxin B has occasionally proved efficacious in some infections due to enterobacilli, such as coli-aerogenes organisms. Colistin is used by some investigators in preference to polymyxin B. If circulatory collapse appears to be too severe to allow intestinal absorption, a tetracycline is given intravenously in amounts of 500 mg. every eight to twelve hours. Alternatively, choloramphenicol sodium succinate, 0.5 to 1.0 gm., can be given intravenously every six to twelve hours. Up to 1 gm. of streptomycin — or up to 0.75 gm. of kanamycin if associated staphylococcal infection or refractoriness appears so to dictate — is given intramuscularly every 12 hours. When polymyxin B is used, a maximal dose of 50 mg. of that drug is given intramuscularly every six hours. If renal function is impaired, less than the maximal amount of streptomycin, kanamycin, or polymyxin B is given in an attempt to avoid accumulation in the blood and consequent enhanced toxicity.

In cases of bacteremia likely due to gram-negative enterobacilli, empiric administration of streptomycin-tetracycline (or chloramphenicol-kanamycin) after samples of blood have been obtained for cultures appears preferable for several reasons. Since identification of bacteria and results of susceptibility tests will not be available for one or more days, the broader antibiotic coverage is desirable. Of the potential pathogens, none are entirely unresponsive to the regimen, and it appears to be an effective regimen against E. coli, the organism most commonly responsible for such infections. An enhanced effect may be obtained from the bactericidal action of streptomycin (or kanamycin) since the tetracyclines (or chloramphenicol) alone are only bacteriostatic.

Danger of Superinfection

Some disadvantages are possible with the empiric use of streptomycin-tetracycline therapy, but these are possible also with alternative antibacterial regimens. The disadvantages include the dual depressive effect on the gram-negative elements of the flora, making superinfection more likely. However, periodic study of smears and cultures of sputum and stools during antibacterial therapy may reveal changes in the flora that might suggest impending superinfection. Streptomycin, kanamycin, and polymyxin B are nephrotoxic; streptomycin and kanamycin are also ototoxic; chloramphenicol is hematotoxic; polymyxin B may cause cerebellar ataxia. In addition, combined therapy entails the introduction of parenteral injections or use of an increased number of injections and is more expensive.

In recent years, it has been our custom, when the patient has progressed favorably, is afebrile, and has a negative initial blood culture after 48 hours of therapy, to discontinue use of streptomycin especially when in vitro tests have revealed bacterial resistance to it, but to continue use of tetracycline until two additional negative blood cultures have been reported and the patient has remained afebrile at least 72 hours. In cases wherein blood cultures are reported as growing certain organisms such as Salmonella, use of streptomycin is discontinued immediately.

Although regard for the potential toxicity of streptomycin should be sufficient to disallow its indiscriminate use, perhaps one should have greater concern for the toxic potential of kanamycin. Kanamycin appears more likely to cause deafness than streptomycin and like dihydrostreptomycin may be responsible for deafness of delayed onset. Streptomycin has the relative advantage of being more likely to cause vestibular damage, which to a considerable degree can be compensated by visual mechanisms.

Members of our group are continuing to use combined streptomycin-tetracycline therapy in these cases for the reasons previously given, as well as in the hope that (1) a series of similar size and employing a different regimen will be reported, or we will accumulate a sufficient number of patients managed differently in our own institution, so that the efficacy of other modes of treatment can be compared, (2) we may evaluate further what may represent a discrepancy between in vitro and in vivo susceptibilities of certain of the causative pathogens, and (3) we may verify or refute our preliminary impression that the regimen produces better results. Since the regimen appears to produce results at least as satisfactory as those reported for other forms of treatment to date, we are not aware of having jeopardized our patients seriously by our choice. Although we have indicated the possibility of an increased incidence of untoward reactions attendant on the regimen, thus far this has not required us to consider abandoning our efforts. In any event, our efforts may provide the stimulus to other investigators to evaluate the regimen selected by us as well as other methods of management.

Occasionally, although empiric therapy is sufficient to prevent death, the response is incomplete; then microbiologic data may indicate possible use of a single agent. Single agents having possible application against certain gram-negative bacilli include (1) penicillin or novobiocin in P. mirabilis bacteremia, (2) chloramphenicol in salmonellosis, and (3) polymyxin B or colistin in coli-aerogenes infections.

Antibiotic for Salmonellosis Typhoid

In regard to salmonellosis, typhoid fever remains best managed with chloramphenicol. Sometimes an initial "loading" dose is given, but the usual maintenance dose is 500 mg. every four hours orally. In bacteremia due to other Salmonella organisms, tetracycline may be preferable. Shigellosis, unlike salmonellosis, almost always is a purely intraluminal enteric infection. However, about 50 cases of Shigella bacteremia have been documented to date. In such patients tetracycline-streptomycin therapy has been suggested.

Other Antibiotics

Ampicillin (Polycillin), a semisynthetic orally administered agent, currently is under investigation for possible use in infections due to strains of E. coli, Salmonella and Proteus. The drug is ineffective against Klebsiella Aerobacter, and Pseudomonas organisms, and, although active against some gram-positive cocci, is less so than penicillin G.[3]

Cephalothin (Keflin), the cephalosporin C. derivative, is active against coli-aerogenes, Proteus, and Klebsiella organisms. The drug

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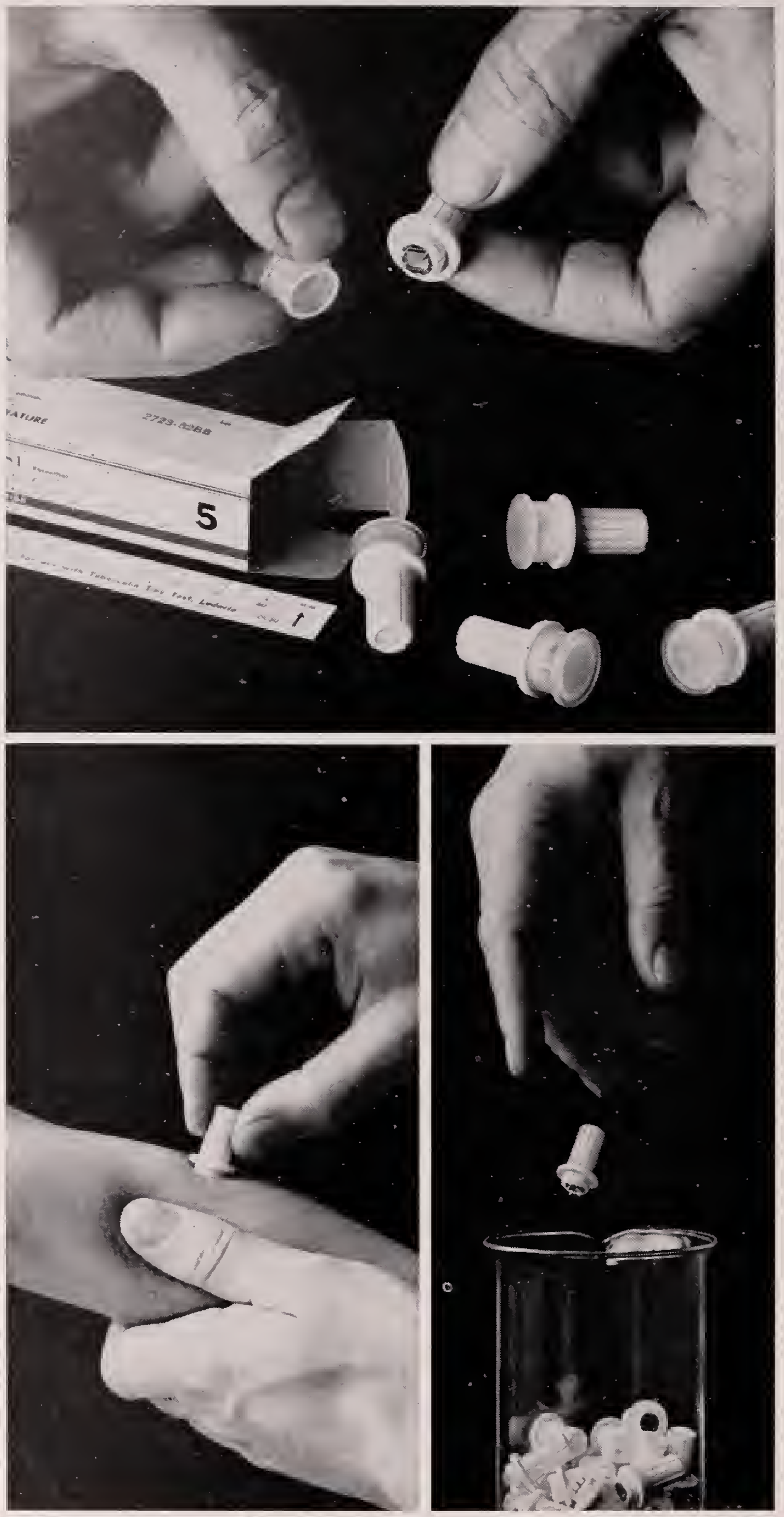

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currently is being investigated in this regard.

Nalidixic acid (NegGram), a naphthyridine derivative, when given intravenously in amounts of 0.5 to 1 gm. several times daily, has been suggested as having potential application in Proteus bacteremia.[3]

Gentamicin (Garymycin) resembles neomycin in its spectrum and like the latter drug is nephrotoxic and ototoxic. Against staphylococci it is cross-resistant with neomycin, and partially so with streptomycin. For systemic effect it is given intramuscularly. Whether gentamicin has application in bacteremia due to gram-negative enterobacilli awaits further investigation.[3]

As a generalization, antibacterial therapy of bacteremia due to enterobacilli should be continued until the patient has been afebrile for at least 72 hours and three successive blood cultures have been negative. More than 70 per cent of our patients having bacteremia due to these bacilli have recovered, despite the fact that one fifth to one third of them experienced bacteremic shock, a complication which increases the mortality rate 10 to 15 per cent. The mortality rate would be considerably less if corrected for such factors as underlying disease, the presence of which probably made recovery impossible in at least half of the fatal cases.

Pseudomonas

In recent years there appears to have been an increase in the incidence of bacteremia due to Pseudomonas organisms. Today, Pseudomonas organisms appear to cause bacteremia about half again as often as Proteus organisms.

Source of Infection

Pseudomonas organisms, although normal inhabitants of the intestinal tract of some persons in small numbers, are also generously distributed in nature and are found in such places as water, on skin surfaces, and in the air. Consequently, these organisms have relatively free access to wounds, drugs, and medical instruments. The increased frequency of Pseudomonas infections may, at least in part, be the result of resistance of the organisms to most of the antimicrobial agents which allows them to emerge as the predominating bacilli when more susceptible bacteria have been eradicated. Notable clinical features may arouse the clinician's suspicion that a given case of bacteremia is caused by Pseudomonas.[12] First are the skin lesions ("ecthyma gangrenosum"), most commonly seen in the anogenital region and axillas, which begin as macules or vesicles, become pustular, and eventually slough to form necrotic ulcers. Ten per cent of our patients having Pseudomonas bacteremia have had such ecthymatous lesions. Another clinical feature worthy of note is marked leukopenia at times associated with thrombocytopenia, as has occurred in 5 per cent of our patients. Jaundice occurs not infrequently in patients having Pseudomonas bacteremia, while bluish-green discoloration of the nail beds is rare.

Treatment

Although polymyxin B remains an effective agent in the management of bacteremia due to organisms of the Pseudomonas group, in some of our cases treatment with other agents, started empirically after blood was obtained for culture, was successful. Our experiences with Pseudomonas bacteremia in patients with advanced malignant, hematologic, disseminated granulomatous, or renal disease corroborate the experiences of others in that no form of current antimicrobial therapy appears to be capable of preventing death in most cases.

Our experience with the newer agent, colistin methate sodium (ColyMycin), in the management of Pseudomonas and in certain gram-negative enterobacillary infections of the bloodstream is not sufficient to warrant a final statement on its possible future application in this regard. Although it is not as bactericidal, weight for weight, as polymyxin B on in vivo testing, colistin is said to have lesser toxicity, but this is disputed. Ampicillin and cephalothin are ineffective against Pseudomonas organisms. Gentamicin is said to be more effective against strains of Pseudomonas than are neomycin or kanamycin.[3]

Bacteroides

Organisms in this family include B. fra-

Continued

gilis, necrobacilli (B. funduliformis), fusospirochetes, and Streptobacillus moniliformis. Members of our group have described some of our experiences with bacteremia due to certain of these organisms.[13] As a generalization, in our experience these organisms cause bacteremia about half as frequently as do Proteus bacilli.

Diarrhea Suggests Bacteroides

Diarrhea beginning before antibiotic therapy and terminating with recovery occurred in one third of our cases.[3] Diarrhea may be noted in cases of bacteremia due to enterobacilli, but classically it suggests causation by members of the Bacteroides family or Salmonella organisms. Failure to obtain anaerobic cultures of the blood may conceal the fact that bacteremia due to members of the Bacteroides family is present. In two thirds of our patients with such bacteremia, incubation times ranged from five to 20 days. Since isolation of the organism required such prolonged incubation of anaerobic cultures, one should observe cultures for three weeks or more before considering them sterile. Because of these peculiarities of Bacteroides, in rare cases of strongly suspected gram-negative bacillary infections of the blood, one is reluctant to discontinue empiric antibacterial therapy until microbiologic investigation has consumed sufficient time to exclude these organisms as being causative. Another finding worthy of note is that in one fifth of our patients with bacteremia due to these bacilli, additional organisms, usually streptococci, were isolated simultaneously. Since certain streptococci may not be responsive to tetracycline, which is the agent of choice in bacteremia due to B. fragilis and necrobacilli, use of an antimicrobial regimen encompassing an anti-streptococcal effect may be required.

Prolonged Therapy

It is our clinical experience, which is supported by the experience of other investigators, that bacteremia due to Bacteroides organisms requires more time for therapeutic control than do gram-negative enterobacillary infections of the blood. If therapy of such bacteremia is not continued for approximately two weeks, the incidence of relapse may be significant. Also, an unexpected delay in clinical response to treatment with appropriate antibacterial agents should suggest the likelihood of a locus of suppuration. As in bacteremia due to Staph. aureus and to Str. pyogenes, metastatic infections are common in bacteremia due to Bacteroides organisms, and surgical drainage may be required in such instances.

As mentioned above, in management of bacteremia due to B. fragilis or necrobacilli, tetracycline is preferred. In cases wherein blood cultures are reported as growing these organisms and the patient has been receiving empiric streptomycin-tetracycline therapy, use of the streptomycin is discontinued. In rat bite fever and Haverhill fever, which are caused by Streptobacillus moniliformis, and in the rare instance of infection of the blood due to fusospirochetes, penicillin is recommended.

Brucella

In patients having bacteremic brucellosis,[14] streptomycin-tetracycline therapy is currently held by many to be the treatment of choice. One method of management consists in giving 500 mg. of a tetracycline orally every six hours and 1 gm. of streptomycin intramuscularly every twelve hours daily for two weeks. Some investigators give a lesser amount of streptomycin and administer the tetracycline for a longer period.

Pasteurella

Tularemia is one of the few diseases in which streptomycin seemingly can be employed alone with excellent results. The tetracyclines also are effective, and in severe cases they have been given conjointly with streptomycin. The same drugs have been effective in plague, but in infections due to certain other Pasteurella organisms, such as Past. multocida, penicillin is recommended.

Hemophilus

In serious infections due to H. influenzae, such as meningitis, invasion of the bloodstream is not infrequent. Tetracycline-streptomycin has been effective; in rapidly progressive infections, chloramphenicol may have special application. Sulfonamides currently are less frequently used.

Achromobacter

Organisms of this family infrequently cause bacteremia; tetracycline-streptomycin is recommended in treatment.

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Alexander Read (Early 18th century)

Alexander Read's distinction rests in large measure on his effort to combine and integrate medicine and surgery, previously two distinct and separate fields, practitioners in each scorning to practice in the other. Read himself was an example of the potentially successful amalgamation of the two, being both a Fellow of the Royal College of Physicians and a member of the Barber Chirugeons, in which capacity he lectured on surgery and wrote a "Treatise on the First Part of Surgery." In this work he laid down the general rules of surgical procedures, digressing occasionally to discuss related matters and even to describe specific operations in detail.

For example, to prove his then-revolutionary theory that a spleen is not indispensable, Read and a colleague removed that organ from a dog. In his own words:

"First an incision was made in the left side hard under the short ribs four inches in length through all the containing parts of the abdomen. Then the spleen was drawn out. Thirdly, all the vessels by which it was bound to the adjacent and contiguous parts we bound to prevent the immoderate flux of blood. Fourthly, we cut away the spleen near to the substance of it. Fifthly, we stitched the parts of the abdomen and left the healing of the parts to nature. All the wounded parts were in a short time healed, but about six weeks afterward the cur was mangy, the spleen belike not drawing into it the feculent blood."*

This splenectomy was probably the first performed in England. So far as we know, there is no record of an earlier one.

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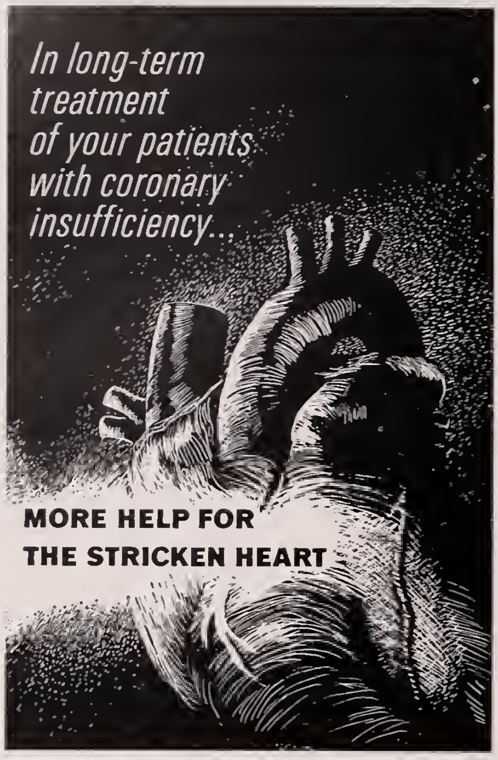
*Parker, G., M.A., M.D., M.R.C.S.: The Early History of Surgery in Great Britain. A. & C. Black, LTD., London, 1920. p. 107.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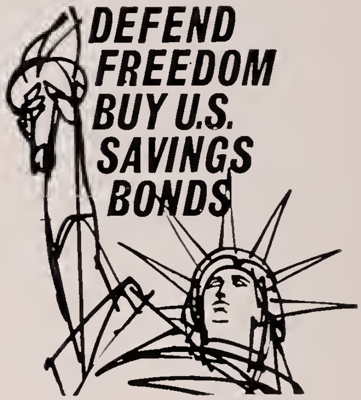
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Grand Rounds

Subclavian Steal Syndrome

Every physician, whether in general practice or in a specialty, encounters in his practice patients with cerebral vascular insufficiency. Cerebral vascular insufficiency represents a disorder of general or localized reduction in blood flow to the brain of sufficient degree to impair normal function.[1] Ischemia of the brain can cause a multitude of symptoms, either transient and reversible in character, or permanent through irreparable damage to nerve tissue.

Present interest is directed toward the study of the potentially reversible forms of cerebral vascular insufficiency. In the past two years, a new clinical entity dealing with stenosis of the subclavian artery proximal to the vertebral artery take-off has been implicated as one of the causes of cerebral-vascular insufficiency through a mechanism that "steals" the blood from the vertebral-basilar arterial system to supply the upper extremity. This phenomenon has been termed the "subclavian steal syndrome."[2,3]

Cerebral Circulation

To briefly review cerebral circulation, the carotid and vertebral arteries form the arterial supply to the brain. The vertebral arteries arise from the subclavian arteries, joining together near the pons to form the basilar artery which in turn gives off the cerebellar, pontine and posterior cerebral arteries in the brain stem before ending at the circle of Willis. The circle of Willis provides important collateral circulation by connecting the basilar and internal carotid systems, especially when major vessels in the head and neck are occluded.[4]

Clinical Manifestations of Cerebral-Vascular Insufficiency

Cerebral vascular insufficiency primarily manifests itself by symptoms of focal neurologic impairment, episodic in character. The main clinical

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*Presented as a Medical Grand Rounds at Mt. Sinai Hospital, Minneapolis, 1/27/64.

Continued

varieties of cerebral-vascular insufficiency consist of recurrent transient ischemic episodes, advancing thrombotic strokes, and complete cerebral infarction.[1] Basically this is due to either partial or complete occlusion of intracranial or extracranial cerebral arteries. Generally, the severity of the symptoms is related to the dysfunction or infarction of critical motor or sensory areas in the brain which are unable to obtain the necessary oxygen for cellular metabolism.

Symptoms of cerebral ischemia depend to a large extent on whether the ischemia is directed toward the carotid artery system or the basilar-vertebral artery system. Widespread occlusive disease may cause both systems to become involved.

Carotid Artery System

The clinical manifestations of carotid artery insufficiency, depending on the hemisphere involved, are those of unilateral muscular weakness affecting either the upper or lower extremity or the facial muscles. The degree of sensory disturbance ranges from paresthesias to marked hypesthesia. Aphasia results if a dominant hemisphere is involved. Transient visual impairment of the ipsilateral eye is the most common ocular symptom. On physical examination, one may find the internal carotid pulsation on the side, contralateral to peripheral involvement, absent or decreased. Occasionally a bruit may be heard at the site of occlusion.

Basilar Artery System

Basilar artery insufficiency involving the brain stem presents a multitude of symptoms, all of which suggest brain-stem ischemia. The most frequently reported symptoms are a shifting bilateral mono- or hemiparesis, diplopia, vertigo, tinnitus, dysphagia, dysarthria, and a transient confusional state. Cranial nerve involvement may be contralateral to motor paralysis. Basilar artery thrombosis with dysphagia, quadraplegia, ocular palsy and coma is usually fatal.[4,5]

Posterior Inferior Cerebellar Artery

One of the more puzzling diagnoses to make and one which may or may not be considered part of the pattern of basilar artery insufficiency, is that of posterior inferior cerebellar artery thrombosis. Mild recurrent episodes of vertigo and paresthesias may preceed the sudden onset of vertigo, ataxia, dysphagia, and contralateral loss of pain and temperature sensation. Horner's syndrome is invariably noted. Usually these symptoms clear spontaneously in several days with varying degrees of residual symptoms remaining.[4]

Differential Diagnosis

The most common cause of cerebral vascular insufficiency is arteriosclerosis. As mentioned, the symptoms of cerebral ischemia need not be directly related to complete vessel occlusion, but only to the degree of cellular dysfunction resulting from the diminished oxygen available for metabolism. Known metabolic and degenerative disease may be present with focal neurologic findings initially. These conditions may be distinguished from cerebral-vascular disorders in that a gradual progression of symptoms is noted with slowly advancing neurological findings. Other diagnoses to be considered in a patient with transient cerebral vascular insufficiency are Meniere's disease, syncope, convulsive disorders, brain tumor, nerve rootlet compression as in cervical osteoarthritis, cervical disc or carpal tunnel syndrome, multiple sclerosis, migraine, and subclavian steal syndrome.[1]

Subclavian Steal Syndrome

Stenosis of extracranial and intracranial vessels comprises most of the pathology involved in cerebral-vascular insufficiency. In 1961 a new clinical entity was reported as a cause.

Reversal of Blood Flow

Reveich[2] reported the first two cases in which symptoms of cerebral ischemia were attributed to a reversal of blood flow down the left vertebral artery in the presence of a stenotic lesion in the left subclavian artery proximal to the vertebral artery take-off. In both cases arteriographic methods demonstrated a retrograde filling from the right vertebral and basilar artery systems into the left vertebral artery. The reversal in flow suggested that a pressure differential existed between the basilar artery system and the junction of the left subclavian and left vertebral arteries. Previously, it had been thought that such a pathway was remote in view of the extensive collateral circulation available to the arm.

Differential Blood Pressure-Right and Left

Clinically, each of these two patients had considerably lower blood pressures in the left arm in comparison with the opposite extremity, with diminished or absent pulses. One of the patients, who complained initially of pain in the left mastoid area, precipitated by exercise and episodes of flaccid left arm paralysis, was noted to have these findings and also a bruit over the left subclavian artery. He subsequently underwent left subclavian endarterectomy to relieve the stenosis demonstrated on the angiograms. During the procedure, a square wave electromagnetic flow meter measured the subclavian artery flow distal to the vertebral artery take-off. With the left subclavian artery occluded proximal to the origin of the left vertebral, measurements taken with the vertebral artery open and occluded demonstrated a reverse blood flow of 120 ml.

The Mechanism of Reverse Flow

Animal experiments were done by Reveich to study the mechanism responsible for the reversal of vertebral artery flow in the presence of left subclavian stenosis. An electro-magnetic wafe flowmeter was placed in dogs to measure blood flow through the common carotid and vertebral arteries. Although the internal carotid artery flow in the dog could not be measured, studies of the internal and external carotids indicated that half the flow of the common carotid was directed to the internal carotid vessel.[6] Blood flow is based on pressure differentials. The basilar artery pressure could not be measured in the dog in this type of experiment, and it was assumed that blood flow in either direction was due to unequal pressures between the vertebral and the basilar arteries. With a cessation of blood flow, equal pressures must exist within the basilar artery and at the

Continued

proximal end of the vertebral artery. In fourteen canine studies, measurements of blood flow following occlusion of the left subclavian artery were taken with a flowmeter. A reversal of blood flow was noted in the left vertebral artery in all the dogs following occlusion of the left subclavian artery, indicating that a pressure gradient existed. As expected, substantial increases in the blood flow of the common carotids and right vertebral artery were noted. Flow increased in the right carotid by 43 per cent and in the left by 45 per cent respectively, while in the right vertebral artery flow increase approached 78 per cent. A significant reduction in cerebral blood flow was found in dogs after occlusion of the left subclavian artery. Overall, total cerebral blood flow decreased 41 per cent despite compensatory increases in vertebral and carotid artery flow.[2]

Comments

The canine studies were consistent with clinical observations in patients with left subclavian artery stenosis and indicated that the pressure differential distal to the subclavian stenosis created a gradient that reversed the vertebral artery blood flow. Reveich coined the term "subclavian steal" to account for symptoms of cerebral ischemia, for blood was indeed being "stolen" into the left subclavian artery at the expense of the cerebral circulation.[2,3]

Other cases of subclavian stenosis subsequently appeared in the literature.[7,8] Mannick[7] reported the case of a 41-year-old factory worker who developed symptoms of left arm and hand claudication, transient attacks of weakness and vertigo while working. A pulseless left arm and absence of blood pressure were noted. Arteriographic studies revealed a reversal of flow in the left vertebral artery. Following endarterectomy, the left arm assumed a normal pulse and blood pressure and the patient had no further symptoms. Apparently this was the first case to suggest that exercise of the arm might precipitate both claudication and cerebro-vascular insufficiency. A second case with right-sided subclavian stenosis was presented in the same article. Previous to this report all documented cases of subclavian stenosis had been left-sided in location.

Massumi[11] reported a case of a six year old child with congenital atresia of the intrathoracic segment of the left subclavian artery in association with a cervical aortic arch. Although symptoms of basilar artery insufficiency were absent retrograde flow down the left vertebral artery was demonstrated by angiograms. This was the first recorded case of a congenital variety of "subclavian steal."

After presenting their findings as to the mechanism of the "subclavian steal" syndrome, Reveich[2] suggested that in cases where surgical ligation of the subclavian artery was contemplated, the ligation be carried out distal to the vertebral artery take-off to prevent a reversal in blood flow. Cases involving surgical repair of traumatic injury to the left subclavian artery, coarctation of the aorta, tetralogy of Fallot, and aortic aneurysm would fall into this category.

The question has been raised by several authors[2,11] as to what happens to the vertebral artery blood flow when a Blalock Taussig shunt is made for correction of tetralogy of Fallot, and the subclavian artery is used as it comes off the aorta. As of now studies of this situation have not been reported.

Treatment

Medical treatment of basilar artery insufficiency has generally been to anticoagulate the patient, use vasodilators, or combine both types of therapy.[5] Medical management with anticoagulants has apparently been beneficial in reducing the mortality and decreasing the number and severity of ischemic episodes secondary to cerebral vascular insufficiency.[12] North, DeBakey, and other vascular surgeons have used vascular reconstruction either by homotransplants of vessels or artificial grafts in an attempt to correct cerebral vascular insufficiency.[9]

Surgical

At present, surgical correction of the left subclavian artery stenosis is accepted as the best method to stop the phenomenon of "subclavian steal" and relieve the symptoms of basilar artery insufficiency. Both Mannick[7] and Reveich[2] have treated their cases this way and have obtained good results with subclavian endarterectomy. Anticoagulants have not been generally used as a long-term treatment in this syndrome.

Case Report

A 56-year-old white female was admitted to Mt. Sinai Hospital because of recurrent severe pain over the left chest of three months' duration. She gave a history of multiple system complaints since 1946 which did not fit any clinical pattern. At that time the patient, living in Kansas, experienced an episode of leg numbness, giddiness, low grade fever, and severe muscle pains. A brucella titre of 1:100 was found and she was given a long series of undulant fever vaccine injections without improvement. She was seen at the University of Minnesota where the diagnosis of Brucellosis was not established after extensive study. The patient's complaints were thought to be functional, and psychotherapy was given with little improvement despite prolonged psychiatric treatment.

Clinical Symptoms

The patient began to experience episodes of giddiness, tinnitus, mild deafness, and right leg numbness. She often experienced a sharp, localized, occipital headache, followed by giddiness, occasional vertigo, marked tinnitus, bilateral hearing loss (at times approaching complete deafness), with various degrees of numbness in the right arm and leg. Some dryness of the eyes and occasional sneezing were noted prior to the onset of symptoms. A majority of these attacks occurred while the patient was carrying on some form of activity during the day, although she did not experience claudication or weakness in the left arm. Numbness and dysthesias in the right arm and leg appeared transiently on occasion without any other symptoms as the patient walked. During these attacks symptoms were moderately relieved by bending her head downward in flexed position. No residuals were noted after these episodes. Extensive diagnostic studies in 1952, 1954, and 1956 failed to disclose any pathology to account for her symptoms. No angiographic studies were done. Three months prior to admission she began having leftsided chest pain, precipitated by exercise, independent of other complaints. These were relieved by sedation and sleep. Electrocardiograms taken on several occasions were normal. The patient had smoked approximatly one pack of cigarettes per day for the past thirty years.

Physical Examination

The patient appeared to be a middle-aged, thin woman who was somewhat nervous but alert and highly intelligent. Blood pressure was 160/94 right arm, with none obtainable in the left arm. There was no arterial pulse in the left subclavicular, left axillary, left brachial, or left radial areas. Normal pulses were noted in the right arm and right supraclavicular region. Bilateral carotid pulses were present. There was no atrophy or color change in the left arm. A constant high pitched thrill was present in the region of the right mastoid, extending to the middle third of the neck. Carotid compression produced a bradycardia, but no syncope or cerebral symptoms were noted. Both femoral pulses were palpable. Neurological examination was negative.

Continued

Laboratory Studies

A chest X ray showed a chronic infiltrate in the right upper lobe which was not present on chest X rays taken in 1956. Intravenous pyelogram revealed a bifid type kidney on the right side. Electrocardiograms were normal. Brucella titre was 1:320. Mantoux, histoplasmosis, blastomycosis and coccidiomycosis tests were all negative. Lupus Erythematosus clot test was negative. Electroencephalogram was negative. A 12 hour creatinine clearance was 91.1 mg. blood cleared per minute. Hemoglobin, leukocyte count, blood sugar, blood urea nitrogen, serum proteins, urinalysis, and cholesterol were normal.

A retrograde aortogram demonstrated retrograde flow in the left verbebral artery and filling of the left subclavian artery from the right vertebral artery. A block to blood flow was demonstated in the left subclavian artery proximal to the take-off of the left vertebral artery. Injection of the right carotid demonstrated congenital atresia of the external carotid artery. The right internal carotid appeared normal, but arteriosclerotic plaques were present without evidence of stenosis. Intracerebral circulation appeared normal.

Summary

Absent pulses and absent blood pressure in the left arm led to angiography with the possibility that the patient had a left subclavian artery stenosis, which was confirmed radiographically with demonstration of left retrograde vertebral artery flow. The patient's symptoms, although somewhat misleading because of the previous diagnosis of "psychoneurosis," were apparently those of true basilar artery insufficiency. She is at present awaiting corrective surgery.

Robert Schneider, M.D.
Intern
Mt. Sinai Hospital

Editors Note:

This is a recently described syndrome which is probably much more common than appreciated by clinicians.

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There are men who would even be afraid to commit themselves on the doctrine that castor oil is a laxative. — Camille Flammarion

Abstracts, Briefs and Commentaries

PELVIC RECURRENCE OF RECTAL CARCINOMA

Local recurrence of rectal carcinoma after surgical excision continues to be a formidable problem. The authors studied the clinical material of the Mayo Clinic in the attempt to understand more about the mechanism of pelvic recurrence.

During the interval of 1952 through 1955, 800 patients were treated by excision for cure. Recurrence has been identified in 92 patients, or about ten per cent. There were undoubtedly others among patients who were not available for follow-up.

Extensive clinical review as well as gross and microscopic tissue analyses were carried out for the patients with known local recurrence. Implantation was thought to be the cause in 27 cases. Direct extension was believed responsible in 10 others. Residual involved lymph nodes, spread through lymphatic channels or peritoneal sedimentation were considered as other likely causes.

Perhaps the greatest improvement is possible in the implantation group. Factors such as gentle handling, sharp dissection, isolation of the tumor bearing segment with tapes when possible, use of iodized gut in anastomoses, and the use of various irrigating agents are discussed.

The case with direct extension may require consideration of more radical excision for certain acceptable candidates.

Diligent post operative follow-up is emphasized, since there is a respectable incidence of new, recurrent, or metastatic lesions in these patients which are amenable to further treatment.

One has only to suffer along with a single patient afflicted with a pelvic recurrence of rectal carcinoma to appreciate the gravity of the problem. The factors discussed in the review which may reduce the incidence of this misfortune are worthy of conscientious application in the treatment of patients with rectal carcinoma. I am sure the authors would concur with a re-emphasis on the need for routine or early digital and proctoscopic exams as a means of achieving detection and treatment in the beginning phases of this disorder.

Robert N. Hammerstrom, M.D.
Minneapolis, Minn.

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AORTIC VALVULAR REPLACEMENT

The authors report on the current findings in 18 patients who survived six to nine months after aortic valvular replacement with Ball valve prosthesis (Starr-Edwards valve). Of the surviving patients, an interesting early postoperative problem was psychological deterioration with overt psychosis which began on the fifth postoperative day and lasted to two weeks. Five such patients had this complication, all five patients recovered. In the late evaluation 13 patients were free of symptoms. Age range of the patients was from 18 to 56 years. The postoperative convalescence varied from three to six months. Six patients had symptoms postoperatively and were not considered to have gained optimum benefit. In one it was felt that there was a significant leak around the aortic prosthesis (aortic regurgitation). Four patients also had diastolic murmurs suggestive of regurgitation but without evidence of significant residual heart distress. Another had auricular fibrillation which was refractory to drugs.

Two charts are presented: these present the preoperative hemodynamic and the postoperative hemodynamic observations. Preoperatively, fourteen patients had recorded pressures within the left ventricle; eight had end-diastolic pressures elevated above the range of normal indicative of heart failure. The postoperative chart indicates that five patients had end-diastolic pressures in the left ventricle above normal limits, again indicative of left ventricular failure. Upon exercise in nine patients the end-diastolic pressure definitely became abnormal in four. In only one case did the end-diastolic pressure go from an abnormal borderline to within a normal range. It is interesting to note that the patients who had the smaller prosthetic valves (9-A, 10-A Starr-Edwards) were also the patients who had the highest transvalvular gradients and left ventricular end-diastolic pressures. Whereas, the patients who had the larger valves had no elevation of the end-diastolic pressures.

In summary, 18 patients were observed to have excellent clinical and hemodynamic findings after operation with replacement of the aortic valve. The authors conclude that the use of this prosthesis affords an opportunity for excellent symptomatic and hemodynamic improvement.

This is a badly needed study which supplies objective data before and after aortic valve surgery. Although not a long-term study, it is of sufficient delay postoperatively to present valuable data as to the hemodynamic course of these individuals. The interpretation of the left ventricular end-diastolic pressure is made by the authors. The interpretation of the end-diastolic pressures in the pressure graph depicted by the authors is difficult to interpret. If the end-diastolic pressure remains abnormally elevated, the long-term results of this type of valve replacement must be very carefully reevaluated. The authors also demonstrate, as had other authors, that there is a significant systolic gradient across the valve, and this must receive continued repeated hemodynamic testing.

Jerome T. Grismer, M.D.
Minneapolis, Minnesota

Bristow, J. D., McCord, C. W., Stahr, M. D., Ritzmann, L. W., and Griswold, H. E.: Clinical and Hemodynamic Results of Aortic Valvular Replacement with a Ball Valve Prothesis. Circulation, 29:35, 1964.

POLYNEUROPATHY — A SYMPTOM FROM INSECTICIDE POISONING

From Salem, North Carolina, Jenkins, Hill, and Toole report two cases of clinical neuropathy attributable to accidental insecticide poisoning. Weakness and paresthesia were the major clinical symptoms, and the physical findings indicate tenderness along the course of nerves. In both instances it was obvious that the individuals had been exposed to unusual quantities of insecticide. DDT, DDD, and Aldarin were the drugs used.

In these two instances no specific therapy was indicated, but the elimination of exposure and a period of hospitalization provided improvement in both instances. From this it can be learned that the important consideration is that of eliminating exposure rather than eliminating the use of insecticides.

Carl O. Rice, M.D.
Minneapolis, Minnesota

Jenkins, R. B., Toole, J. F.: Polyneuropathy Following Exposure to Insecticides. Int Med 113:691, 1964.

DUODENAL FISTULA

Artificial, fairly large, two-by-three centimeter defects were made in the lateral duodenum of dogs and the fistula allowed to establish. Then the defect in the duodenum was closed primarily, and the jejenum, either from a Roux-Y or adjacent loop, was sutured over the closure as a serosal patch reinforcement or support. The serosal patch principle is also applied to cases where the fistulous defect is too large to close primarily. One case is cited of clinical success in a patient.

The technic of "serosal patch" here described appears to be a useful simplification, another tool in the handling of difficult GI tract surgical problems.

J. H. Strickler, M.D.
Minneapolis, Minnesota

Wolfman, Earl F., Jr., M.D., Trevino, Guillermo, M.D., Heaps, David K., M.D., and Zuidema, George D., M.D.: An Operative Technic for the Management of Acute and Chronic Lateral Duodenal Fistulas. Ann Surg 159:563, 1964.

ARTERIAL INJURIES

Repair of arterial injuries has decreased the amputation rate to 15% from the 50% which prevailed when ligation was practiced. Methods of treatment include lateral repair, resection of damaged area with end-to-end anastomosis, and resection and graft, with or without the assistance of partial or complete cardiopulmonary bypass. Lacerations of large arteries (aorta, iliac) may be treated by lateral repair. Lacerations of smaller arteries are best treated by resection and anastomosis, or by resection and graft. Arteriovenous fistulas and true and false aneurysms are best treated by resection and restoration of blood flow. "Spasm" in an artery is frequently due to intimal rupture or subintimal hemorrhage, and also requires resection and anastomosis in many instances. Clinical examples of each type of injury are presented. Angiography is of great value in establishing the precise abnormality present, its location, the degree of collateral circulation, and the result achieved by surgery.

Courtesy of References and Reviews
Journal of the American Medical Association

MacLean, L,
Canad Med Ass J 88:1091 June 1 1963

ALDOSTERONISM

This article summarizes the clinical findings, the diagnostic methods employed, and the surgical results in twelve patients with primary aldosteronism. The clinical syndrome is of hypertension, hypokalemia, and metabolic alkalosis.

First, increased aldosterone production increases Na+ retention; second, it increases K+ and H+ urinary excretion; third, despite an increased H+ excretion, an alkaline urine results from excessive NH+ excretion; and fourth, renal damage eventually occurs, with polyuria, polydipsia, easy fatigability and intermittent weakness.

All 12 patients had hypertension (nine months to sixteen years), hypokalemia, an associated hypernotremia and elevated serum CO_2. On low sodium diet, urinary aldosterone levels were elevated in 11 individuals; but urinary 17 hydroxycorticosteroids and 17 ketosteroids were normal. Five patients had impaired renal function.

Differential diagnosis includes:

A) Secondary aldosteronism from obligatory renal loss of sodium (salt-losing nephritis).
B) Ischemic renal disease.
C) Essential malignant hypertension.
D) Hypokalemia from other causes.

Helpful diagnostic tests are:

1) Low sodium diet, which elicits a decrease in Na+ urinary excretion in primary aldosteronism. In salt-losing nephritis, Na+ loss continues despite a marked increase in aldosterone secretion and excretion. This is a most valuable test.
2) Administration of salt-poor albumin consistently reduces excretion of aldosterone in secondary, but produces no change in primary aldosteronism.
3) Aldosterone antagonists do *not* differentiate between primary and secondary disease.
4) Potassium loading may distinguish between types of hypokalemia as loading stimulates and depletion reduces aldosterone secretion.
5) Renal arteriography may be needed to distinguish ischemic renal problems.

About 80% of patients with primary aldosteronism have an adrenal cortical adenoma. Carcinoma is rare; hyperplasia comprises the remaining group.

In Cushing's syndrome, 70% of patients have hyperplasia.

Bilateral adrenal exploration through a transverse abdominal incision was the preferred surgical approach. The results of surgery are usually good.

The article is difficult to read because of assumptions by the author. However, the bibliography contains an excellent article written by one of the authors. Hence the combination of the articles proves truly helpful.

Jerome T. Grismer, M.D.
Minneapolis, Minn.

Gilbert, J. W., Bell, N. H., Bartler, F. C.: Primary Aldosteronism, Diagnosis and Surgical Treatment. Ann Surg 158:195 1963

THE SOLITARY THYROID NODULES

The authors present an interesting analysis from a selective group of relatively young persons with thyroid nodules studied at the U.S. Navy Hospital in Portsmouth, Virginia. They found the overall group to have an 18% incidence of carcinoma of the thyroid. However, when the nodule was clinically evaluated as being a solitary nodule, the incidence of carcinoma grows to 20%. The ability to accurately evaluate nodularity between solitary and multiple.

Forty-one of 120 patients thought to have solitary nodules in reality had multiple nodules. However, of 79 actually proven solitary nodules, the incidence of carcinoma was 26.5%, whereas in the proven multiple nodules the carcinoma incidence was only 8.5%.

Preoperative scintiscanning was performed on 119 of these patients. Fifteen cold nodules had an incidence of 27.7% cancer, so that a separation between benign and malignant tumors is rather difficult, having only less than one-third accuracy. If the cold nodule were considered to be likely malignant, the separating of solitary and multi-nodular goiters is also difficult on this basis. Two out of four hot nodules on scintiscanning were malignant. This is not statistically significant, but it does emphasize the fact that a hyper-functioning nodule is not uniformly benign.

The authors do conclude, however, that a hypo-functioning or normally functioning nodule that is soft and mobile to palpation would warrant a six week trial period on desiccated thyroid with regression of size as index of its benignancy. They further suggest that multiple nodular glands are suitable for trial of thyroid therapy unless a clinically suspicious area exists.

J. H. Strickler, M.D.
Minneapolis, Minn.

Grant, H. T. H., Center, J. W., and Lenhardt, H. F.: The Enigmatic Thyroid Nodule. Ann Surg 158:205, 1963

COMBINATION THERAPY IN INOPERABLE BRONCHOGENIC CARCINOMA

One of the prospects for the improvement of results in cancer therapy is the combined use of a chemotherapeutic agent and external radiation therapy. Statistics indicate that 6 out of 100 persons with lung cancer will be alive after 5 years. These 6 are early diagnosed cases where removal of the tumor was possible. The inoperable cases are considered incurable, the usual therapy used is external radiation which slows the growth and alleviates symptoms, but very seldom results in a cure.

Twenty-six patients with inoperable lung cancer were randomized. Thirteen were treated with external radiation alone and 13 were treated with a combination of intravenous 5-fluorouracil plus external radiation therapy. The average mean survival of the group treated with radiation only is 6.2 months. The longest survivor lived 14 months. The average mean survival of the group treated with 5-fluorouracil plus external radiation is 16.8 months, with three living survivors of 40, 43, and 50 months.

The series is small, but a statistically significant gain is achieved. Further studies are being carried out with the use of combination therapy in lung cancer and other malignancies.

Frank F. Gollin, M.D.
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SPONTANEOUS PERFORATION

Spontaneous perforation of the bile ducts is rare. McWilliams reported 90 cases of biliary peritonitis, in which 10% were due to nontraumatic perforation of the bile ducts. In some cases no abnormality of the duct system could be demonstrated.

The authors report a female, 77 years of age, who entered the hospital with acute abdominal complaints of 12 hours duration. Examination revealed findings indicating exploratory laparotomy. At surgery a large quantity of free clear bile was found. The gall bladder was pathologic. Other organs were negative. Bile had extravasated retroperitoneally along the lesser omental harsa and into the porta hepatis. The main bile ducts were explored by dissection and no leak discovered until the gall bladder was compressed and a fine jet of bile escaped at the junction of the cystic and common ducts. A T tube was introduced and the gall bladder removed. It contained two stones. Convalescence was uneventful. Postoperative cholangiogram was normal.

The authors reviewed the literature and conclude that unexplained cases of bile peritonitis may be due to pin-point perforations not found at surgery. A list of likely causes of such perforations suggested by McWilliams in 1912 are cited: (1) "Intramural infection with necrosis of the duct wall; (2) Thrombosis of mural vessels with necrosis of the duct wall; (3) Activation of reflux pancreatic secretion and digestion of the wall. Cope in 1925, stated that the histology of the bile ducts reveal numerous mucous glands embedded in the wall, some of which penetrate the thin muscle into the subserous layer. If one of these glands becomes distended by occlusion of its opening, it may present as a small cyst on the surface. If intraductal pressure builds up as a result of the passage of a stone or due to a spasm of the sphincter of Oddi, the bile could escape thru this apt and result in peritonitis. This could account for a number of so-called idiopathic bile peritonitis cases.

The study of individual patients with all clinical means at hand may not demonstrate fistula due to disease primarily in the biliary or the digestive tract. In most instances the severity and extent of the pathology of the surgical cases can be determined only after abdominal exploration. Bile must be restored to its passage into the digestive tract; stones must be removed from the ducts, and the duct patency established. If malignancy causes obstruction, some type of short circuiting becomes imperative. On one occasion in the presence of massive carcinoma of the pancreas I was able to get a T tube through the mass, which was effective during the patient's survival. Another very elderly and very ill patient with obstruction high in the small bowel due to a single nonfacetted stone unfortunately did not survive operation.

In the second paper the finding of the leak by pressure on the gall bladder was of interest. The suggested process by which a ductal gland produced a channel through the wall of the duct, after it had formed an cyst, sounds feasible. The bile peritonitis of patients that I have seen in consultation has been the aftermath of biliary surgery.

Stanley R. Maxeiner, M.D.
Minneapolis, Minnesota

Harris, W. G., Shoesmith, J. Harrop: Spontaneous Perforation of the Bile Ducts. Brit J Surg 50:425, 1963.

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SURGERY FOR SUPERFICIAL THROMBOPHLEBITIS

Although superficial thrombophlebitis is generally considered a somewhat innocuous disorder, the authors believe an aggressive surgical approach is often the preferred method of treatment. They have compared a group of 92 patients having superficial thrombophlebitis treated surgically with 243 patients similarly afflicted who were treated non-surgically. Surgery consisted of high saphenous ligation, with or without vein stripping. Six patients, however, required vena caval and three patients required femoral ligations for pulmonary emboli which occurred while on nonoperative management.

In this series the total incidence of pulmonary embolism in superficial thrombophlebitis was 10%. Ten patients had emboli preoperatively. None occurred postoperatively.

In addition to the prevention of embolization the authors find surgery permitted much earlier ambulation with a more rapid resolution of symptoms.

As a result of this study the authors recommend elastic supports with ambulation for superficial phlebitis below the knee. Medications for pain relief or to suppress inflammation may be used for the patient's comfort. Thrombophlebitis above the knee or that not responding to the above regimen should be treated by ligation. Vein excision may be included depending on the extent of varicosities and the patients condition.

There is a surprisingly high incidence of pulmonary embolization reported in this study. Either there are a significant number of deep vein thromboses included or we will have to assume a greater respect for superficial thrombophlebitis. In any event, the impressive results of the surgical treatment in these patients warrant renewed consideration of the place of surgery in management of superficial thrombophlebitis.

Robert N. Hammerstrom, M.D.
Minneapolis, Minnesota

Williams, R. D., and Zollinger, R. W.: Surgical Treatment of Superficial Thrombophlebitis. SGO 118:745, 1964.

PROSTHETIC REPLACEMENT OF MITRAL VALVE

This is an excellent article in which the authors describe their experience in 22 patients who ranged in age from 19 to 50 years. Patients were considered to be in Class III and IV according to the New York Heart Association classification system. The valvular lesion consisted of mitral stenosis and/or mitral regurgitation. Mitral valvular calcification was present in 13 patients, auricular fibrillation in 19 patients, and tricuspid regurgitation in 14 patients. Eighteen of the 22 patients survived the procedure. Two patients required a second operation to close regurgitant orifices between the valve ring and the annulus of the heart.

The authors presented charts of heart catheterization at preoperatively and postoperatively in these individuals. The studies indicate that the Starr-Edwards prosthetic mitral ball valve served as an effective substitute for the diseased human valve. In all patients the hemodynamic abnormalities regressed postoperatively. However, the studies also demonstrated that the design of the valve is imperfect and a definite gradient existed between

Continued

the left atrium and the left ventricle which gradient was magnified at the time of exercise.

As a result of this, the authors recommended changes in the design of the Starr-Edwards valve. The redesigned valve provides a larger hydraulic orifice to the valve.

This is one of the fine articles that has presented objective physiologic data of the preoperative and the postoperative status of patients undergoing mitral valvular replacement. Of the 22 patients studied only twenty patients had resting pulmonary artery pressures considered above the limits of normal. Two patients with normal pressures had evidence of a significant gradient across the mitral valve. It is also interesting to note that in the patients who had predominantly mitral insufficiency, there was no gradient across the mitral valve despite a high pulmonary artery pressure in four of the 11 cases presented. This type of evaluation of preoperatively and postoperatively is sorely needed in patients undergoing closed mitral valvular commissurotomy. Such objective data will enable a "natural history" of a postoperative patient to evolve.

Jerome T. Grismer, M.D.
Minneapolis, Minnesota

Morrow, A. G., Clark, W. D., Harrison, D. C., and Braunwald, E.: Prosthetic Replacement of the Mitral Valve-Operative Methods and the Results of Preoperative and Postoperative Hemodynamic Assessments: Circulation. 29:2, 1964.

KIDNEY CYSTS AND NEOPLASMS

During a 3-year period at a urological clinic, 80 aortograms were made, of patients who had an expanding renal mass. In five of them, with aortograms negative for kidney tumors, a renal neoplasm was found at operation or autopsy. The microscopic diagnoses in these cases were tubular adenoma in one patient, carcinoma of the kidney in two, cystadenocarcinoma in one, and renal papillary cystadenoma with papillary carcinoma of the bladder in one. The two patients with renal carcinoma died, but the remaining three were alive and free of recurrences when this report was written, at 8, 9, and 11 years after surgical treatment. The cases reported point to the unreliability of renal arteriography as a basis for differentiating between kidney cysts and neoplasms. The findings indicate that: (1) certain renal tumors cannot be accurately diagnosed by aortography; (2) in the interpretation of aortograms, it is of primary importance to rely only upon positive findings; (3) in the presence of a negative aortogram, surgical exploration of a kidney mass is recommended as the most dependable diagnostic method; and (4) only in the presence of an expanding renal mass, where it is important to obtain additional information which may change the therapeutic course, should an aortogram be done.

Courtesy of References and Reviews
Journal of the American Medical Association

Uson, A., Melicow, M., and Lattimer, J.: J Urol 89:554 April 1963

It is better to deserve without receiving, than to receive without deserving.
— Robert Ingersoll

Book Reviews

Every man is a volume if you know how to read him. — Channing

CANCER OF THE FEMALE REPRODUCTIVE ORGANS — **Alfred I. Sherman, M.D., C. V. Mosby Company, St. Louis, 1963. 338 pp. 70 illustrations and 21 tables.**

In addition to a discussion along traditional lines of each of the gynecologic malignant diseases usually included in a book of this kind, the author has prepared valuable chapters on the nature of malignancy, radiophysics, persistent cancer, chemotherapy, surgical technique, nursing care and survival statistics.

The chapter that discusses the use of radiation therapy in cancer is basic and will capture the interest of even the most clinically oriented. It is a prelude to the outstanding chapter in the book on carcinoma of the cervix. This chapter, which comprises more than one-third of the book, devotes over 50 pages to an excellent detailed discussion of radiotherapy but only six pages to surgical and five pages to combined therapy. It is obvious that the author's main interest is radiation therapy of this disease.

The remainder of the book, although current and objective, does not quite measure up to the quality of the previously mentioned chapters. There are fewer illustrations and occasional typographic errors. Those who expect to find detailed discussions of surgical techniques applicable in the treatment of gynecologic malignancy will be disappointed.

Despite the minor deficiences noted, the gynecologist or radiologist who seeks general knowledge of gynecologic malignant disease and the application of radiation therapy to gynecologic malignancy, especially in the treatment of carcinoma of the cervix, will find this book a valuable addition to his medical library.

Konald A. Prem, M.D.
Minneapolis, Minnesota

OTOLARYNGOLOGY — **David D. DeWeese, M.D. and William H. Saunders, M.D. C. V. Mosby Company, St. Louis 1964. 523 pages. 405 figures. $9.25**

This textbook of Otolaryngology is well edited, with sufficient photographs and line drawing illustrations to make it of value to the student, the general practitioner, and the doctor who wishes to have a book on otolaryngology in his library for quick reference.

It contains 32 chapters and these are well arranged.

A short but adequate bibliography is available at the end of each chapter. The index might have been a bit more extensive.

As a surgeon I find it a good reference source in my library.

Carl O. Rice, M.D.
Minneapolis, Minnesota

AGING IN MINNESOTA — **Arnold M. Rose, 1963 by the University of Minnesota Press.**

This book is an outgrowth of the preparations in Minnesota for the 1961 White House Conference on Aging. The text presents a rather comprehensive review of the problems of senior citizens and some of the measures taking place, or recommended, to solve these problems. There is considerable historical material presented which gives the reader a prospective as to the problem of the aging citizen and what has been done in the past. Most of the material pertains to senior citizens in the state of Minnesota. A very comprehensive analysis of 1700 elderly citizens is presented in one of the chapters and is excellent reference material for those particularly interested in the problems of the elderly. A rather long, but very interesting and perceptive essay is included by Aldena Carlson Thomason who is now herself a senior citizen of 80 years. The reader will obtain considerable insight into the feelings and situation of the elderly from this very excellent introspective discussion. This book should be required reading for persons in the field of social service and sociology, and physicians dealing largely in geriatrics. However, physicians in all fields will find it interesting and informative reading.

Dr. Alvin Schultz
Mt. Sinai Hospital
Minneapolis, Minn.

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Perinatal Mortality Study

Delayed Treatment

The mother in this case report was 40 years old. This was her 10th pregnancy. She had eight living children, her last pregnancy having resulted in abruptio placentae with delivery of a stillborn infant. At 28 weeks of gestation her blood pressure was 104/74, and at 32 weeks 168/88. She showed no abnormal weight gain. At 32 weeks her hemoglobin was 75%.

At 9:30 A.M. on the day of admission (34 weeks of gestation) she had bright red, painless vaginal bleeding, estimated at three to four cups. When she was admitted at 12:10 P.M., her blood pressure was 80/40, hemoglobin 8.4 gm.%, hematocrit 26%, and fetal heart tones 120 and faint. The fibrinogen index showed no clot after 60 minutes with only thin fibers present. She was given 500 cc. dextran 6% along with 1000 cc. 5% glucose in water. Five hundred cc. of blood were added at 1:20 P.M., which brought her blood pressure to 120/66 at 2:00 P.M.

She continued to bleed heavily and by 2:40 P.M. had saturated eight pads; her blood pressure had fallen to 86/52, and the fetal heart tones were 152. Five hundred cc. more blood were added. At 3:30 P.M. her blood pressure was 92/54, and the fetal heart tones were 132 and irregular. At 4:30 P.M. the fetal heart tones were absent and remained absent thereafter.

A fetogram X ray on the day of admission was interpreted to indicate 28 weeks of gestation and marginal placenta previa.

No vaginal examination was made.

At 5:00 P.M., the day of admission, the mother was given another 1000 cc. of 5% glucose in water, which brought her blood pressure to 112/50. She continued to pass bright red vaginal blood, and by 11:00 P.M. her blood pressure had fallen to 70/42. Her hemoglobin was checked at 11:00 P.M. and found to be 7.4 gm.%. She was then given one unit of packed cells, also 1000 cc. 5% glucose in water. Her bladder was catheterized at 1:20 A.M., the day following admission, with only 20 cc. obtained. (Her last catheterization had been at 5:00 P.M. the day before with 180 cc. obtained.) Amniotomy was done at 1:55 A.M.; at 2:25 A.M. slow pitocin drip was started with delivery of the stillborn infant, occiput anterior, at 3:46 A.M. the day following admission. The infant weighed 1000 gm. and measured 14 inches in length. The placenta measured 15 x 13 cm., and at one edge there was a ragged defect in the maternal surface measuring 7 x 4 cm. The mother left the hospital four days after delivery, at which time her hemoglobin was 7.4 gm.%. She refused a transfusion and was given 2 cc. Imferon I.M.

Autopsy of the infant seven hours following delivery revealed the following:

> Petechial hemorrhages over the heart, lungs and thymus. Small amounts of blood within the subcutaneous tissues of the scalp with a

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*Hennepin County Perinatal Mortality Study Committee.

Continued

subperiosteal hematoma over the left parietal bone. No evidence of intracranial hemorrhage. Microscopic sections of the lungs showing atelectasis and small amounts of aspirated amniotic fluid within the alveolar spaces. Remainder of microscopic sections within normal limits.

Comment

The Hennepin County Perinatal Mortality Study Committee feels that the mother should have received proper management as outlined in the *Suggested Guide For Obstetric Hospital Practice.*[1]

The Management of Placenta Previa

1. If complete or central placenta previa is demonstrated by careful vaginal digital examination, the termination of pregnancy by cesarean section is indicated.
2. The management of lesser degrees of placenta previa requires judgment. Some cases may require termination of the pregnancy by cesarean section and others may require only simple rupture of the fetal membranes. Choice of the method of treatment should be made by evaluating such factors as parity, the condition of the cervix, the status of the fetus, and the degree of placenta previa demonstrated.

The Management of Premature Separation of the Placenta

If the history and an examination (including, if necessary, a sterile vaginal examination) lead to a diagnosis of premature separation of the placenta, the following appropriate measures are advised:

1. Blood should be made available for the replacement of significant blood loss.
2. Consultation is indicated.
3. Five to ten grams of fibrinogen should be made available.
4. *Clot observation tests* should be done hourly, as follows: Five cc. of blood are drawn and placed in a small test tube. At adequate fibrinogen levels, a firm clot forms which does not lyse during a period of 30 minutes. With a critical lowering of plasma fibrinogen, no clot forms. Between these levels, the formation of a soft clot which lyses in less than 30 minutes indicates a serious fibrinogen depletion.
5. If clot observation tests reveal significant fibrinogen depletion, two grams of fibrinogen should be administered and the dose repeated as shown necessary by hourly tests. This should be done even though the patient is not bleeding.
6. If the fetus is living and viable, and delivery, as judged by the state of the cervix and the character of the labor, is not imminent, blood loss should be replaced and a cesarean section should be performed.
7. If the fetus is living and viable, and delivery is imminent, simple membrane rupture should be done and shock should be controlled by blood replacement.

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[1] *Suggested Guide for Obstetric Hospital Practice* approved by Minnesota State Medical Association, Minnesota Chapter of General Practice, Minnesota Obstetrical and Gynecological Society. Available from Minnesota Department of Health, Section of Maternal and Child Health, University Campus, Minneapolis 14, Minnesota.

8. It may be advisable to stimulate labor by instituting an intravenous Pitocin drip after membrane rupture has been accomplished.

9. If intravenous Pitocin drip is used to stimulate labor, it should be continued post partum until the danger of hemorrhage has passed.

10. If the fetus is dead, conservative management is usually indicated.:
    a. Rupture of the membranes should be carried out as soon as it is practicable.
    b. The replacement of blood loss should be made.
    c. The institution of an intravenous Pitocin drip may be required to stimulate labor.

11. If the fetus is dead, radical management with delivery by cesarean section is indicated only on rare occasions in the presence of severe abruptio placentae when the probability of vaginal delivery being accomplished within a reasonable length of time is unlikely.

12. Every attempt should be made to correct shock before resorting to delivery by cesarean section.

Conclusions

The Committee feels that the following should have been done:

1. The mother should have had a vaginal examination. 2. She should have received continuous adequate blood. 3. She should have received fibrinogen when her fibrinogen index revealed no clot after 60 minutes. 4. Repeat fibrinogen tests should have been done. 5. She should have had an amniotomy early rather than waiting until almost 14 hours after admission. 6. She should also have had early obstetric staff consultation.

The Committee hopes that this case and the Guide[1] will stimulate better obstetric care.

Compromise is odious to passionate natures because it seems a surrender, and to intellectual natures because it seems a confusion; but to the inner man, to the profound Psyche within us, whose life is warm, nebulous and plastic, compromise seems the path of profit and justice. — George Santayana

A house is no home unless it contain food and fire for the mind as well as for the body. — Margaret Fuller

The man who has a house everywhere has a home nowhere. — Martial

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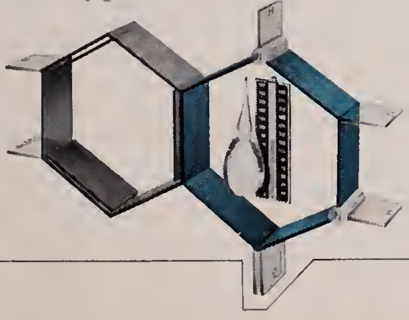

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SIDE EFFECTS: Skin rash (rare), gastrointestinal disturbances, weakness and dizziness, seldom so severe that drug should be stopped. Generally, the adverse effects sometimes associated with the thiazide diuretics are possible. Pre-existing electrolyte abnormalities may be aggravated.

CONTRAINDICATION: Anuria.

1. Steigmann, F., and Griffin, R.: Evaluation of Quinethazone, a New Diuretic. J. Amer. Geriat. Soc. 11:945 (Oct.) 1963.

2. Schwartz, M.: Office Evaluation of a New Diuretic in Patients with Hypertensive Diseases. Scientific Exhibit Presented at the Clinical Meeting of the American Medical Association, Los Angeles, California, Nov. 25-28, 1962.

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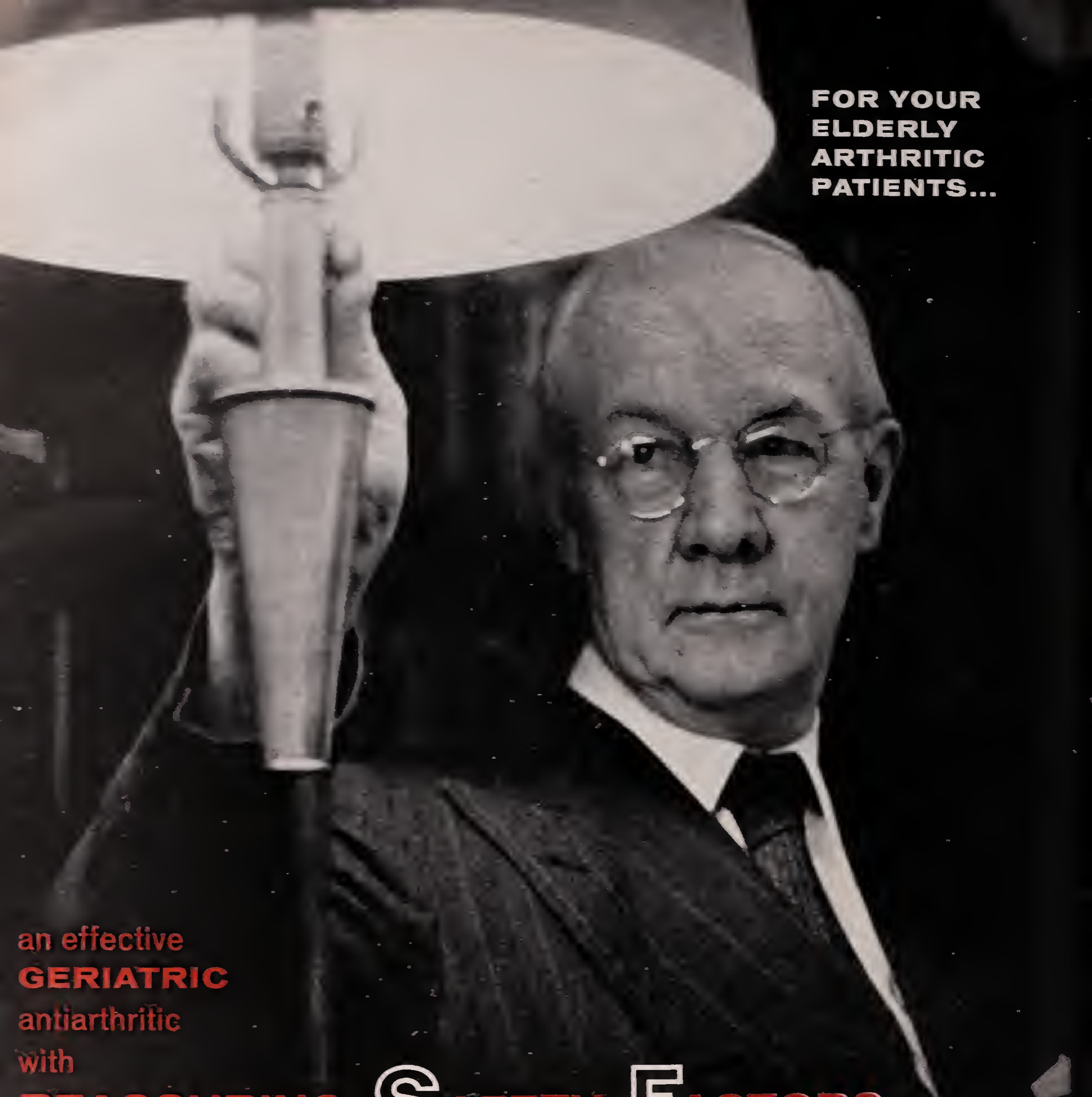

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REASSURING SAFETY FACTORS

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Side Effects: Occasionally, mild salicylism may occur, but it responds readily to adjustment of dosage. Precaution: In the presence of severe renal impairment, care should be taken to avoid accumulation of salicylate and PABA. Contraindicated: An hypersensitivity to any component.

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Meetings and Announcements

A man should live with his superiors as he does with his fire; not too near, lest he burn; nor too far off, lest he freeze.—Diogenes

OCTOBER

First National Congress on Strokes, October 29-31, Palmer House in Chicago. Contact. AMA in Chicago.

American College of Nutrition, Americana Hotel in New York City, October 25. Contact: Robert Peterman, M.D.; 3 Craig Court; Totowa Boro, New Jersey 07512.

American College of Gastroenterology, October 19-21, Roosevelt Hotel in New York City. Write: American College of Gastroenterology, 33 West 60th Street, New York, New York.

American College of Physicians postgraduate course, October 19-23, University of Wisconsin Medical Center at Madison. Topic: "The Medicine of Tomorrow." Write: College; 4200 Pine Street, Philadelphia, Pa.

University of Colorado postgraduate Chiefs of Staff Conference October 22-24 in Denver. Write: University; 4200 E. Ninth Avenue; Denver.

Mound Park Hospital Foundation and the AMA postgraduate course on "Modern Concepts of Nutrition and Heart Disease," St. Petersburg, Florida, October 22-24, in the Auditorium of the Mound Park Hospital. Contact: Nutrition, Mound Park Hospital Foundation, Inc.; St. Petersburg, Florida 33701.

American Medical Association Second Annual Community Health Week will be observed October 18-24. All media will encourage recognition of the achievements of medicine and public health during this week.

American Electroencephalographic Society, Bishop's Lodge, Santa Fe, N. M., October. Sec: Kenneth A. Kooi, M.D., University of Michigan Medical Center, Ann Arbor.

NOVEMBER

University of Illinois College of Medicine at the medical center will conduct a postgraduate course in laryngology and bronchoesophagology, November 9-21. Write the University; 1853 West Polk Street, Chicago 60612.

AMA Sixth National Conference on the medical aspects of sports, Deauville Hotel, November 29, in Miami Beach, Florida. Write: AMA, Chicago.

Milwaukee Medical Conference on "Medical and Surgical Aspects of Trauma," November 11-12, Milwaukee County Hospital, Coffey Auditorium. Write: Medical Society, 756 N. Milwaukee Street; Milwaukee.

National Society Convention for Crippled Children and Adults, November 13-16 at the Statler-Hilton Hotel, Detroit. Contact: Society; 2023 West Ogden Avenue; Chicago.

AMA Second National Congress on Mental Illness and Health, November 5-7 in Chicago, Palmer House. Contact: Council; 535 North Dearborn, Chicago.

Annual Meeting of Section of Otolaryngology of the Southern Medical Association, November 16-19, Memphis, Tenn. Contact: Neil Callahan, M.D.; 506 Professional Building; Portsmouth, Virginia.

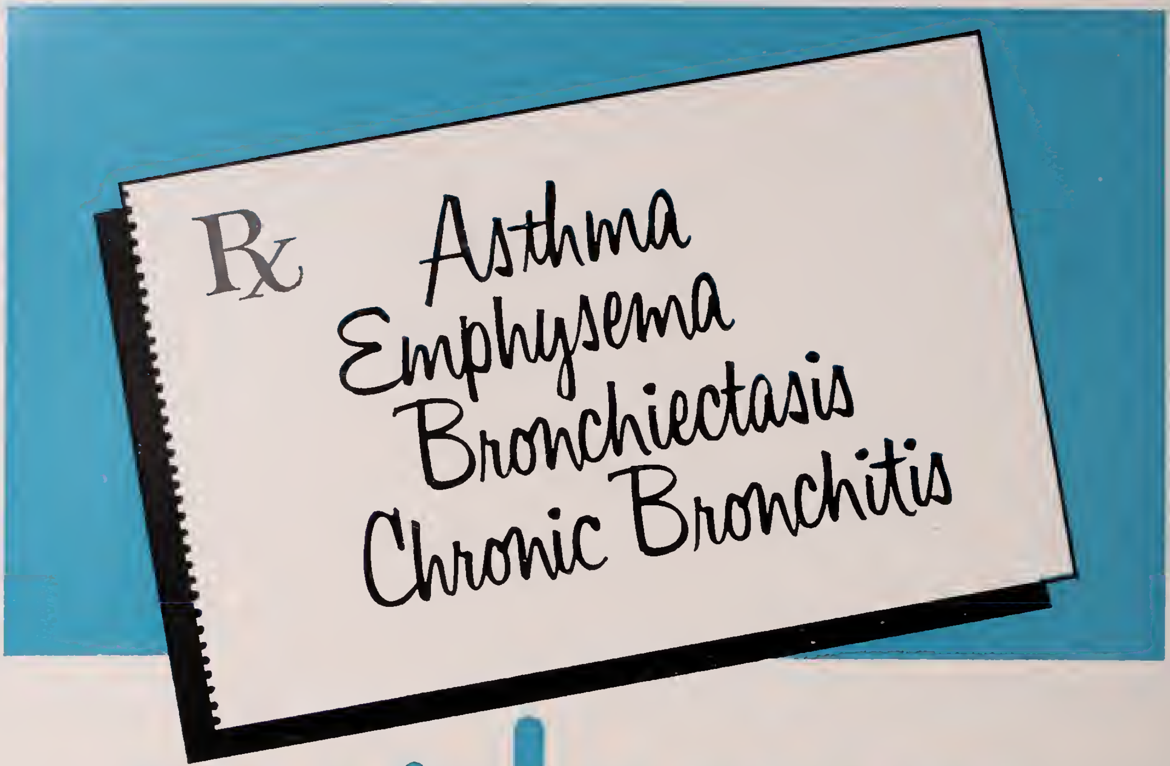
Seventeenth Annual Conference on Engineering in Medicine and Biology, Cleveland at the Sheraton-Cleveland Hotel, November 16-18. Contact: Dr. David Fleming, Case Institute of Technology, Cleveland.

ANNOUNCEMENTS

Applications being received for Wyeth Pediatric Residency Fellowships that will begin on July 1, 1965. Each fellowship provides $4800 over two years toward advanced study required for board certification. Information: Dr. Philip Barba, University of Pennsylvania School of Medicine; Philadelphia, Pa. 19104.

* * *

American Society of Oral Surgeons announces presentation of cash awards for manuscripts concerning any phase of research related to oral surgery completed during the current year. Write: American Society of Oral Surgeons, 919 North Michigan, Chicago.



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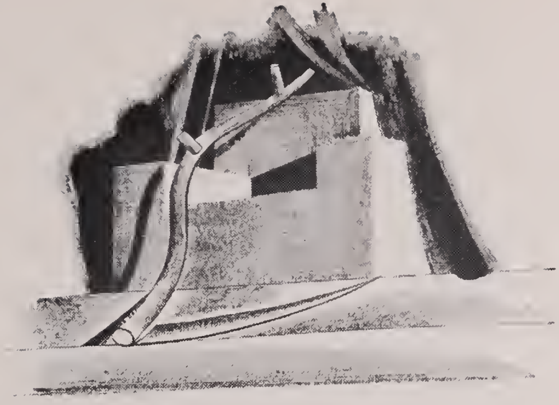

In Memoriam

It matters not at what hour the righteous fall asleep. — Death cannot come untimely to him who is fit to die. — The less of this cold world the more of heaven, the briefer life, the earlier immortality.—Milman

HARRY A. JOHNSON

Dr. Harry A. Johnson, 62, Edina physician and surgeon, died August 23rd. He was on the staff of St. Barnabas hospital and former chief of the staff of St. Andrew's hospital. A graduate of Gustavus Adolphus College, St. Peter, Dr. Johnson received his medical degree from the University of Minnesota.

He was a member of the president's council of Gustavus Adolphus, Hennepin County Medical Society, Minnesota State Medical Association, American Medical Association, Pan-Pacific Surgical Society, Zuhrah Temple of the Shrine, Edina American Legion Post, Navy League, Minneapolis Athletic Club, Svenska-Sallskapet Society, and Parents Association of Carleton College.

He is survived by his wife, a son, Dr. Harry A. Johnson, Jr. of Chicago and three daughters.

HARRY G. IRVINE

Dr. Harry G. Irvine, 82, a member of the University of Minnesota medical faculty for forty-four years and a pioneer in the eradiction of venereal diseases, died August 24th. He was born at Portland, Maine, brought to Minnesota as a baby, and graduated in 1903 from the University of Minnesota Medical School.

He was a member of the Hennepin County Medical Society and American Medical Association and a life and 50 Club member of the Minnesota State Medical Association.

He is survived by his wife, son and a daughter.

CLYDE EARL WILSON

Dr. Clyde E. Wilson, 79, physician and community leader for fifty-one years in Blue Earth, died August 9th. He was born in Pilot Grove township and graduated from the University of Illinois medical school in 1912.

Dr. Wilson was a member of the Blue Earth City school board for forty years, and in January of this year, the Minnesota Education Association presented him the distinguished service award as the state's outstanding school board member. He had been president of the Blue Earth Valley Medical Society, was a member of the American Medical Association, chairman of the county Red Cross chapter, director of the Community club, president of the Kiwanis Club, was a Mason, had been county coroner for many years, and was a life and 50 Club member of the Minnesota State Medical Association.

He is survived by his wife and two daughters.

ALEXANDER M. WATSON

Dr. Alexander M. Watson, 80, general practitioner in Royalton, died August 28 after a short illness. He was born at Quebec, Canada and graduated from the University of Western Ontario, Canada.

Dr. Watson practiced medicine for fifty-six years, and during this time served as district director of the Minnesota Public Health Department, mayor of the village, master of the local Masonic lodge. He was a member and a past president of the Upper Mississippi Medical Society, member of the American Medical Association and a life and 50 Club member of the Minnesota Medical Association.

He is survived by his wife and three sons, two of whom are Dr. Sidney W. Watson of Royalton and Dr. Robert M. Watson of Morris.

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Side Effects: Occasionally, mild salicylism may occur, but it responds readily to adjustment of dosage. Precaution: In the presence of severe renal impairment, care should be taken to avoid accumulation of salicylate and PABA. Contraindicated: An hypersensitivity to any component.

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The Blue Shield

National Blue Shield Not Fulfilling Role

Blue Shield has done an unexpectedly good job in coordinating and administering its nationwide service-benefit plan, which now covers 56% of all U. S. civil service workers, says Andrew E. Ruddock, director of the U. S. Civil Service Commission's Bureau of Retirement and Insurance. Yet, he asks: "Is Blue Shield truly a service-benefit program?"

Ruddock addressed the National Association of Blue Shield Plans at their annual business meeting in Hollywood, Florida, early in April.

To make it an honest-to-God service-benefit program, Ruddock would like to see the Blue Shield Plans drop their income limits. He'd like participating physicians to accept as full payment — for all federal government patients — scheduled fees based either on a relative value scale or on customary charges within a community. He would like the Plans to shoot for the more immediate and attainable goal of raising minimum family income ceilings for federal workers from $6,000 to $7,500.

Ruddock is influential because he speaks for 3,600,000 Blue Shield subscribers and dependents enrolled in the federal employee health benefits program. The program, as he pointedly reminded the delegates, sends a check for roughly $8½ million to Blue Cross & Blue Shield twice a month — more than $3 million of that amount winding up in the pockets of individual practitioners throughout the country.

Will Blue Shield Extend Benefits?

Judging by the reaction of Blue Shield higher-ups, Ruddock will get a large measure of the increase next fall, when contract-signing time rolls around. A reference committee report, delivered to Plan executives two days after Ruddock's speech, endorsed his appeal wholeheartedly. It urged member Plans "to raise income levels applicable to the federal employee program to $7,500 and to make corresponding and appropriate adjustments in fee schedules related to such programs."

The unanimous approval of higher income ceilings is indicative of a general trend in Blue Shield thinking away from cash indemnities and toward uncompromising service benefits.

The federal employee program looms large, not simply because it's Blue Shield's biggest customer, but because it's widely regarded as a showcase plan — an impressive display of Blue Shield capabilities.

Many provisions of the original contract — e.g., treatment for mental illness and tuberculosis — were considered daring four years ago. Now they're fairly common with Blue Shield Plans around the country. The government's insistence on extended benefits stirred Blue Shield to come up with a modern major medical policy; the number of member Plans offering such coverage has since doubled.

Flaws Developed

But an example can demonstrate weaknesses as well as strengths. If flaws develop within the showcase plan, they are apt to be symptomatic of what ails the Blue Shield Plans in general. The flaws are:

The income limit — the percentage of federal workers who qualify for paid-in-full benefits has been shrinking rapidly. Due to pay raises, the 73% of federal employees within the $6,000 income limit in 1960 dropped to 67% in 1961 and to 60% the following year. By this fall, only 49% will have salaries of $6,000 or less.

Through an accident of geography — two out of every five government workers aren't assured service benefits and may have to pay surcharges to their doctors over and above insurance benefits. (They're in areas where Blue Shield doesn't guarantee service benefits — including most of Ohio — Ed.)

If those two factors — income ceilings and service areas — remain unchanged, Ruddock predicted, Blue Shield's showcase plan will soon be offering guaranteed service benefits to less than 30% of its subscribers.

Blue Plans Aware of Difficulties

The men who run Blue Shield are well aware of the built-in difficulties posed by service benefits. Indeed, they anticipated and sympathized with the government request for higher income ceilings far in advance of the annual business meeting. Still, they feel the picture isn't as black as Ruddock paints it.

Continued to Page 1313

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M.M.

History of Medicine

William Osler

1849-1919

The influence of William Osler has left deep traces in the history of medicine. No medical man in America has been so deeply revered. Canadian born, of Celtic extraction, the son of a clergyman, Osler took his degree at McGill University in 1872, and studied abroad in London, Berlin, and Vienna. His post-graduate courses grounded him well in histology and physiology, plus the advantage of becoming familiar with German clinical medicine and laboratory research. Returning to Canada in 1874, he began his medical career as professor of medical institutions at McGill. During his ten years there, besides doing outstanding work in pathology and biology, Osler rapidly gained a reputation as a distinguished clinican. In 1884 he accepted a summons to become professor of clinical medicine in the University of Pennsylvania. "The five years spent in Philadelphia were fruitful, enabling Osler to reach his full stature as clinician, teacher, and writer."[1] A fortunate circumstance in his career was the opening of the new Johns Hopkins hospital in 1889, with the medical school ready to open its doors in 1893. Osler was called to the post of Physician-in-Chief.

His textbook, THE PRINCIPLES AND PRACTICE OF MEDICINE, which he wrote in 1891, had undoubtedly through its many editions greater influence on the teaching of medicine in this country than any other book. "The publication of his text-book not only ensured him immortality as a medical writer, but also precipitated one of the major events in his life — his marriage . . . his future wife, the widow of Dr. Samuel Gross of Philadelphia, refused to have him until the book was finished. Finally he threw a copy of the book into her lap with the remark: 'There, take the darn thing: now what are you going to do with the man?' They were married . . . on 7 May 1892, and never did any man choose a wife who could better fill the role of partner in a life utterly devoted to the cure and comradeship of fellow beings . . . Grace Revere Osler . . . was always content to subordinate her life to his."[2] Throughout the years she was a gracious hostess to the throngs of students and physicians from all over the world who came to their home.

The sixteen years at Baltimore were the fullest of Osler's life. "His work in the organization of the new medical clinic at the Johns Hopkins Hospital in 1889, his insistence that for the proper care of the patient as well as for the improvement of the teaching of medicine, the student should be used, . . . as an assistant in the wards, his practical abandonment of barren, old didactic methods, were steps of great importance in the advancement of medical instruction. . . ."[3] There was an aura about the beloved "Chief." "He was one of Nature's chosen . . . a sunbright personality . . . an Appollonian poise, swiftness and surely of thought and speech, every gift of the gods was his; and to these were added careful training, unsurpassed clin-

Continued

Of 1,028 patients with confirmed respiratory infections... 954 or 92.8% were treated successfully with Signemycin®

Note:

Hammerl* selected his patients for treatment with Signemycin on the basis of demonstrated bacteriological resistance to other antibiotics or failure of previous therapy. Of 100 patients with various respiratory tract infections, 95 responded to Signemycin. Pathogens isolated included staphylococci and *Diplococcus pneumoniae.*

*Hammerl, H.: Wien. Med. Wschr. 108:629, July 26, 1958.

Condition	No. of Patients	No. Cured with Signemycin
Abscess, pulmonary	17	16
Bronchiectasis	19	13
Bronchitis	286	267
Bronchopneumonia	192	179
Empyema	12	11
Pneumonia, lobar	150	146
Pneumonia, other febrile	160	150
Various infected pneumopathies	192	172
Totals	1,028	954 (92.8%)

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Brief Summary and Bibliography follow.

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ical ability, the widest knowledge of his subject, the deepest interest in everything human, and a serene hold upon his fellows that was as a seal set upon them. His enthusiasm for his calling was boundless. As Hare says, 'Osler went into the post-mortem room with the joyous demeanour of the youthful Sophocles leading the chorus of victory after the battle of Salamis.' "[4]

His teaching in the classroom and dispensary was a memorable experience for his students. Always informal, he often sat on the edge of the table with one leg swinging free. "The students knew he liked a joke and hence had the temerity to wear sweetpeas in their buttonholes when the exercise dealt with diabetes."[5] In his "observation clinic" as he called it, "The students would line up on two rows of chairs, a couch for the patient between them. Osler would come into the room in buoyant spirits and sit at the head of the couch, and a student would present the history of the case. . . . The patient would then be examined by Osler and the student . . . to teach the beginners how to look at, feel, and listen to a patient, and how to observe the manifestations of disease. . . . Although the primary object was observation of the patient, the students perhaps unconsciously learned much from watching the great physician — how he put the patient at ease with kindly words and jest, his delightful sense of humor, his keen analysis. . . . Osler devoted every Saturday evening to his students. The group on the medical wards was invited to his house . . . gather around his dining-room table and listen to his unsurpassed talk on medical history. . . . The fact that Osler gave up one evening every week from his busy life . . . shows his devotion to his students and his strong desire to give them spiritual nourishment and to plant seeds of medical culture from his abundant store in their minds."[6]

References

1. Franklin, Alfred White, Editor: Selected Writings of Sir William Osler, Oxford University Press, xvi, 1951.
2. Ibid, xvii.
3. Thayer, William Sydney: Osler and Other Papers, The Johns Hopkins Press, 7, 1931.
4. Garrison, Fielding H.: An Introduction to the History of Medicine, W. B. Saunders Co., 683, 1922.
5. Pratt, Joseph H.: A Year with Osler, The Johns Hopkins Press, xiii, 1949.

To be Continued in November issue

Soap and water and common sense are the best disinfectants. — William Osler

A mother takes twenty years to make a man of her boy, and another woman makes a fool of him in twenty minutes. — Robert Frost

A man's action is only a picture book of his creed.—Emerson

Of 1,021 children with various confirmed infections... 950 or 93.0% were treated successfully with Signemycin®

Note:
The effectiveness of Signemycin was demonstrated by Chattas and his co-workers* who administered Signemycin to 30 children with serious staphylococcal infections resistant to commonly used antibiotics. Only one failed to respond. In each case the use of this drug was indicated by antibiogram. Those children treated with a nonselected antibiotic—for comparative purposes—took three times longer to recover.

Chattas, A. et al.: Antibiot. Med. 7:300, May, 1960.

Condition	No. of Patients	No. Cured with Signemycin
Eye, ear, nose, throat infections	368	343
Respiratory infections	369	346
Gastrointestinal infections	42	30
Skin and soft-tissue infections	38	37
Deep-seated or generalized infections	47	44
Various conditions	157	150
Totals	1,021	950 (93.0%)

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Robitussin with antihistamine and codeine

Each 5 cc. (1 tsp.) contains:

Glyceryl guaiacolate	100 mg.
Pheniramine maleate	7.5 mg.
Codeine phosphate	10.0 mg.

(Warning: may be habit forming)
Alcohol 3.5 per cent

Robitussin is indicated in coughs associated with head and chest colds, bronchitis, laryngitis, tracheitis, pharyngitis, pertussis, "flu," "grippe," measles, chronic paranasal sinusitis, pulmonary tuberculosis, or smoking. Robitussin A-C is especially indicated for allergic, harsh or unresponsive coughs.

dosage: ADULTS—1 tsp. every 3 to 4 hours. CHILDREN—½ tsp. every 3 to 4 hours.

side effects: No serious side effects from glyceryl guaiacolate have ever been reported. Nausea, G-I upset, and drowsiness may be encountered rarely with Robitussin A-C.

precautions: There are no contraindications for Robitussin. Robitussin A-C is contraindicated in patients hypersensitive to antihistamines or codeine.

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antihistaminic / antitussive

Each 5 cc. (1 tsp.) contains:

Dimetane® (brompheniramine maleate)	2 mg.
Phenylephrine hydrochloride	5 mg.
Phenylpropanolamine hydrochloride	5 mg.
Glyceryl guaiacolate	100 mg.

Alcohol 3.5 per cent in a palatable, aromatic base.

DIMETANE® EXPECTORANT-DC (exempt narcotic)

antihistaminic / antitussive / suppressant

Codeine phosphate (Warning: may be habit forming)	10 mg.
Dimetane® (brompheniramine maleate)	2 mg.
Phenylephrine hydrochloride	5 mg.
Phenylpropanolamine hydrochloride	5 mg.
Glyceryl guaiacolate	100 mg.

Alcohol 3.5 per cent in a palatable, aromatic base.

Indicated for relief of cough and allergic states in which an expectorant action is useful. Dimetane Expectorant-DC is indicated when the cough suppressant action of codeine is desired.

dosage: ADULTS—1 to 2 tsp. q.i.d., as necessary. CHILDREN—½ to 1 tsp., t.i.d. or q.i.d.

side effects: Overdosage may result in mild drowsiness or excitement, but within the therapeutic range neither is likely.

Precautions: Administer with caution to patients with cardiac or peripheral vascular diseases and hypertension.

contraindications: Hypersensitivity to antihistamines or codeine. Not recommended for use during pregnancy.

references:* Boyd, E. M., and Ronan, A. K.: Am. J. Physiol., 135:383, 1942.

minnesota medicine

MEDICAL ASSOCIATION

Volume 47

Number 11

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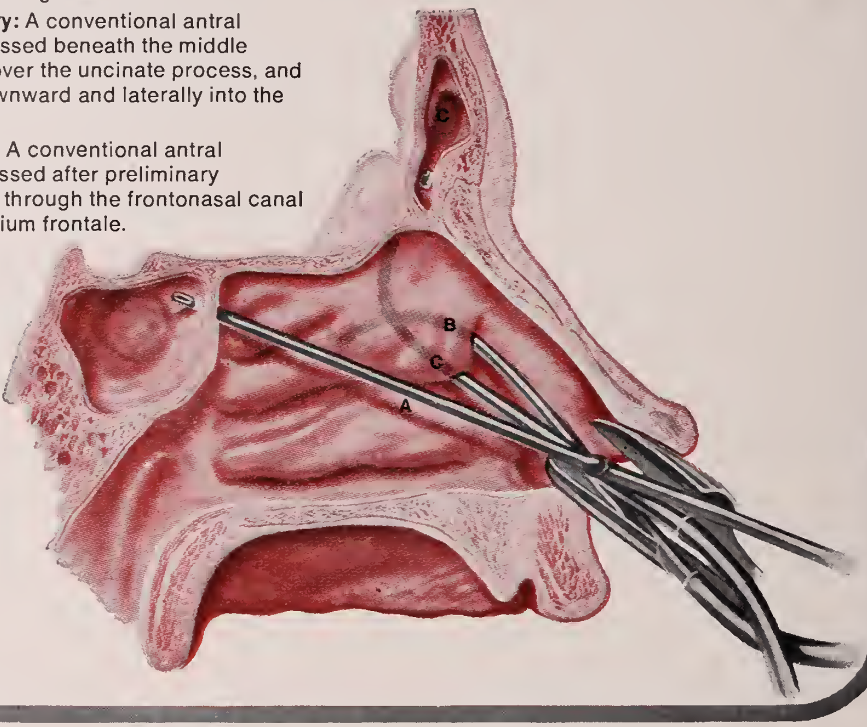

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*Reed, G. F.: Sinusitis, New England J. Med. 267:402, Aug. 23, 1962.

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President's Letter

Unfortunately, the medical profession is plagued as are all other groups by a small percentage of members who fail to recognize, or refuse to abide by, accepted standards of conduct. Our Minnesota statutes name specifically some types of behavior which are unacceptable. Our lawmakers apparently were aware of the futility of attempting to specify all grounds providing for the revocation or suspension of a license. The law simply states that "immoral, dishonorable, or unprofessional conduct" constitutes justification for such severe disciplinary action.

The Minnesota State Board of Medical Examiners realizes the implications of license revocation or suspension to an individual physician. It reserves this step for those completely recalcitrant doctors of medicine who literally drive it to that extreme. All others, erring but reasonable physicians, are given the benefit of the Board's rehabilitative efforts.

The success of this policy can be measured by observing the generally high standards of practice in Minnesota in contrast to the relatively few revocations or suspensions. Do not think that I am cavalier in my attitude. I know, as well as the next fellow, that improper (but not necessarily reprehensible) things go on. But the physician's appraisal of his peers must always be tempered with reasonable judgment. For instance, when did you last roll by a *Stop* sign?

Lines are hard to discern. The Supreme Court of the State of Washington finds, for instance, that a physician who wilfully evades part of his income tax is subject to license revocation because this offense involves moral turpitude. In Maryland, on the other hand, it is held that the crime of income tax evasion does not involve moral turpitude, and the offense is not a sufficient basis for revoking a license. But in Ohio moral turpitude is not even an issue. There, the physician convicted of the same offense may have his license revoked because he is guilty of a felony. This example points out the difficulty of defining unprofessional conduct in the generic sense.

The Supreme Court of New York has said: "What constitutes unprofessional conduct must be determined by those standards which are commonly accepted by those practicing the same profession in the same community." And the Supreme Court of the United States says this: "It is fitting that the physician should possess a knowledge of diseases and their remedies, but also that he should be one who may be safely trusted to apply these remedies. Character is as important a qualification as knowledge." According to the dictionary unprofessional conduct is "that which violates the ethical code of the profession, or such conduct which is unbecoming a member of a profession in good standing," from which we can conclude, I suppose, that unprofessional conduct is conduct which reflects adversely on the reputation of the profession and its practitioners.

The Executive Secretary of your Association, legal counsel for the Association, members of the State Board, and legal counsel for the Board have discussed mutual prob-

Continued on page 1431

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Purpura

● The
● Allergic
● Aspects

E. J. WALTER BOWIE,, B.M., B.Ch.
ALBERT B. HAGEDORN, M.D.*
Rochester, Minnesota

TYRIAN PURPLE was a dye obtained from a species of mollusks called purpura, which has given its name to the purple discoloration of the skin that results from intracutaneous bleeding. Purpura takes the form of ecchymoses or petechiae. Bruises or ecchymoses may be seen in most types of bleeding diatheses, but petechiae, the pin-point areas of hemorrhage from capillary loops, are most suggestive of vascular or platelet abnormalities.

In a review of the numerous types of purpura, it is apparent that many of them have allergic aspects. Purpura usually is divided into the thrombocytopenic and the nonthrombocytopenic purpura, and the allergic types of purpura are found in both categories. This paper will confine itself to a discussion of some of the allergic aspects of purpura.

Anaphylactoid Purpura

Schönlein[1] described purpura with acute rheumatic symptoms (peliosis rheumatica), and Henoch[2] noted its association with gastrointestinal manifestations. Renal, central nervous system, and cardiac involvement also may occur, and the whole syndrome has been included under the generic name of anaphylactoid purpura.[3]

The characteristic rash starts as an erythematous macule, which finally becomes purpuric. The platelet count is usually normal or slightly reduced, and the bleeding seems to be due to a capillary lesion. Biopsy of skin in a region of the rash shows a marked perivascular infiltration with polymorphonuclear leukocytes, macrophages, and lymphocytes, and the disease is generally accepted as an allergic angiitis. The etiology is controversial. An upper respiratory infection commonly precedes the explosive onset of purpura by two or three weeks. In only one third of the cases,[4] however, is the antistreptolysin O titer raised, which suggests that the beta-hemolytic streptococcus may be of less importance than previously supposed. Drug and food allergies have also been proposed as etiologic agents.

It has been suggested that Henoch-Schönlein purpura is an autoimmune disease. Attempts have been made to document this experimentally, and purpura of the nonthrombocytopenic type has been produced by the injection of vascular endothelium antiserum into animals.[5] Stefanini and Mednicoff[6] demonstrated a precipitin reaction between the sera of some patients with anaphylactoid purpura and the extracts prepared from human aortic intima. In most cases, however, no definite etiologic factor can be demonstrated convincingly.

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*Section of Medicine, Mayo Clinic and Mayo Foundation.

Idiopathic Thrombocytopenic Purpura

In idiopathic thrombocytopenic purpura, there is no obvious primary cause for the thrombocytopenia. Usually the megakaryocytes in the bone marrow are present in normal or increased numbers, and generally the spleen is not palpable. The disease can be considered as having acute and chronic forms. The acute form is self-limiting and more common in persons in their first two decades of life, but both forms of the disease can occur in a person of any age. The cause is unknown, but it has been proposed that the disease is due either to an inhibition of platelet release from the megakaryocytes or to an increased destruction of platelets in the peripheral blood or the spleen. The former hypothesis is supported by the observation that within 24 hours after splenectomy the megakaryocytes begin to release platelets.

Antiplatelet Factor

The experiments of Harrington and associates,[8] however, have shown convincingly that there is an antiplatelet factor in the plasma of some patients with idiopathic thrombocytopenic purpura. Harrington transfused himself and others with whole blood and plasma from patients with idiopathic thrombocytopenic purpura, and an alarming decrease in platelet count accompanied by purpura developed.[8] It has subsequently been shown that a decrease in platelets can be obtained by transfusions of normal plasma, but the decrease is much less striking than that produced by plasma from patients with idiopathic thrombocytopenic purpura.[9]

In children born of mothers with idiopathic thrombocytopenic purpura, there is a thrombocytopenia that gradually clears within six weeks. This clearing may occur even in the offspring of women who have been splenectomized,[10,11] suggesting that an antiplatelet factor has passed from the maternal to the fetal circulation. It has also been shown that the life span of platelets is reduced in idiopathic thrombocytopenic purpura[12] as a result of platelet destruction in the circulating blood or the spleen.

The concepts of megakaryocyte inhibition and of increased platelet destruction are not mutually incompatible, and a combination of both factors probably produces the thrombocytopenia. In a few of the patients investigated by the Cr^{51}-labelling method for measuring platelet lifespan, such a combined mechanism has been demonstrated.[13,14]

Antibody and Autoimmunity

The existence of an antiplatelet factor seems well established, but its nature is still open to question. The concept that an antibody is involved and that the disease is an autoimmune one is supported by the Evans-Fisher syndrome in which thrombocytopenia occurs in conjunction with a Coombs' positive hemolytic anemia.[15] It has never been shown convincingly, however, that the factor is an antibody. Platelet agglutination tests are difficult to interpret because aggregation is a normal function of platelets. Tests such as the antiglobulin consumption tests, the mixed agglutination test, and the C^{14}-serotonin test have not consistently demonstrated antibodies in idiopathic thrombocytopenic purpura. The recent work of Jackson and his colleagues[16] has shown that thrombin may cause platelet aggregation that is indistinguishable from the immunologic phenomenon of agglutination. If prothrombin is removed from the serum by barium sulphate adsorption, the results of the platelet agglutination tests in many cases of idiopathic thrombocytopenic purpura become negative.

Purpura due to Drug Reaction

Both thrombocytopenic and nonthrombocytopenic purpura may be related to drug hypersensitivity.

The mechanism of action of the drugs that causes thrombocytopenia as a result of peripheral destruction of platelets has been elucidated particularly by the work of Ackroyd[17] with Sedormid and quinidine. Ackroyd[17] stated the belief that the drug acts as a haptene and, in combination with a platelet protein, stimulates the formation of antibody with resulting platelet agglutination. In the presence of complement, lysis occurs. It has also been suggested that the drug combines with a protein in the plasma to form antibody and that this drug protein complex becomes attached to the platelet with resulting agglutination and lysis.[18,19] Moeschlin and Wagner[20] have proposed that, in agranulocytosis due to aminopyrine and sulfapyridine, it is the resulting antibody that combines with the leukocytes. A similar mechanism may apply to platelets.[21]

Abnormal Gamma Globulin

The work of Dausset[21] has shown that Sedormid is removed from solution by platelets in vitro and that antibody is adsorbed only by platelets that have been in contact with Sedormid. This is good evidence in favor of Ackroyd's theory. It has been clearly shown that the abnormality lies in the serum of a sensitized patient and that this is an abnormal gamma globulin. These two factors together with the observation that the gamma globulin causes fixation of complement and subsequent platelet lysis suggest that the gamma globulin is most likely an antibody.

Numerous other drugs have been reported to cause thrombocytopenia, among which are quinidine, quinine, chlorpheniramine maleate, phenazone derivatives, insulin, aspirin, codeine, phenobarbital, aminopyrine, and antazoline.

Drug sensitivity may also result in purpura in the presence of a normal platelet count. It has been shown that an antigenic similarity exists between capillary endothelium and platelets.[22] It is interesting to note that patch-testing in a patient with sensitivity to Sedormid results in a local petechial reaction, due to capillary sensitivity in spite of a normal platelet count. Many drugs have been reputed to produce purpura in the presence of a normal platelet count; these include iodides, belladonna, atropine, quinine, bismuth, mercury, penicillin, aspirin, phenacetin and chloral hydrate. One of the most interesting drugs in this regard is carbromal (diethyl-bromo-acetylcarbamide).[23] This drug is structurally related to Sedormid, which is allyl-isopropyl-acetylcarbamide (Figure).

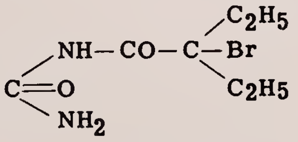
Nevertheless, the use of carbromal results only in a capillary reaction, whereas Sedormid may cause thrombocytopenia as well.

Purpura of Unusual Origin

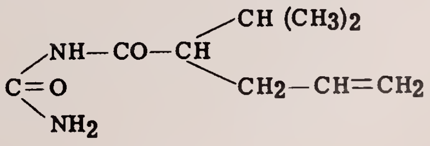
*Gardner-Diamond Syndrome**

In the syndrome of Gardner and Diamond,[24] the patient usually gives a history of severe trauma or of an extensive surgical procedure. Painful ecchymoses appear on the limbs after the trauma or surgical procedure and may become quite extensive. In one patient we have observed, both breasts were eventually destroyed by the process. The disease nearly always occurs in women; these women often have a disturbed emotional background. There has been recent interest in the relationship of the psychiatric situation to the occurrence of the purpura.[25] From the work of Gardner and Diamond,[24] the purpura appears to be caused by the patient's sensitivity to the stroma of her own red blood corpuscles. Widespread hemorrhagic manifestations, including intracerebral hemorrhage, have been seen in some patients.

One patient with the Gardner-Diamond syndrome had a three-year remission after splenectomy,[24] but the remission is difficult to evaluate, as the disease has naturally occurring remissions. Corticosteroids and anti-



Carbromal
(diethyl-bromo-acetylcarbamide)



Sedormid
(allyl-isopropyl-acetylcarbamide)

Structural formulas of carbromal and Sedormid.

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*See page 1332 for syndrome explanation.

malarial drugs have also been tried with variable results. Desensitization procedures were of little help in Gardner's original cases.

Deoxyribonucleic Acid Hypersensitivity

Deoxyribonucleic acid hypersensitivity was first described by Levin and Pinkus.[26] Their patient had severe painful ecchymoses on the extremities, and skin biopsy showed hematoxylin bodies. These hematoxylin bodies may be seen in lupus erythematosus, although this was the only suggestion of lupus. Because the lupus erythematosus cell factor has antideoxyribonucleic acid properties, the possibility that the patient may be sensitive to her own deoxyribonucleic acid was suggested and subsequently proven by skin tests. The response to chloroquine was convincing. Schwartz and his colleagues[27] have reported another case with a similar response to chloroquine.

Summary

Purpura has a multitude of possible causes, and in a few instances the intracutaneous bleeding is of allergic etiology. The various types of purpura that have some allergic aspects and that are discussed in the paper are: anaphylactoid purpura, idiopathic thrombocytopenic purpura, purpura due to drug reaction, and purpura associated with the Gardner-Diamond syndrome and deoxyribonucleic acid sensitivity.

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10-27 May be obtained from author or the reprints.

GARDNER-DIAMOND SYNDROME

The Gardner-Diamond syndrome is also known as the syndrome of autoerythrocyte sensitization. It was first described by Gardner and Diamond* in 1955, and is a type of chronic purpura seen exclusively in adult females. There is nearly always a history of extensive trauma. One of the characteristics of the purpura is that the ecchymotic areas are painful, a symptom which may be very troublesome. Gastrointestinal bleeding, hematuria, and rarely intracranial bleeding may occur. Attention has been drawn recently to the psychiatric makeup of these patients, and the suggestion has been made that this syndrome is a psychophysiologic entity.** The diagnosis is confirmed by the production of the characteristic ecchymosis by an intradermal injection of the patient's own red cells. It has been shown that these patients are sensitive to the stroma of the red cells. The syndrome of DNA hypersensitivity*** is clinically indistinguishable.

---

*Gardner, F. H. and Diamond, L. K.: Autoerythrocyte Sensitization. Blood 10:675, 1955.

**Agle, D. P. and Ratnoff, O. D.: Purpura as a Psychosomatic Entity: Psychiatric Studies of Autoerythrocyte Sensitization. Arch Int Med 109:685, 1962.

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HARRY W. SOUTHWICK, M.D.*
Chicago, Illinois

Malignant Melanoma

How Much Surgery

OVER THE years one of the most disturbing and yet one of the most challenging of the malignant tumors is the malignant melanoma. It is disturbing because for so long the salvage rate was so poor; it is challenging because it is an obvious, accessible lesion that should be amenable to early diagnosis and adequate management. Perhaps it is unfortunate that every pigmented spot on the white human race is not of such a nature that it is immediately suspect and subjected to eradication. To implement this suggestion, however, would require the undivided time of all of the members of the Minneapolis Surgical Society practically for the rest of their lives. Under the circumstances, however, we find ourselves, of necessity, removing the pigmented lesions from the palms of the hands and the soles of the feet, removing lesions that are cosmetically unattractive, and finally removing those lesions that become suspect because of their changing size, color, ulceration, and so forth.

It is encouraging to note that even the application of these ground rules has gradually improved the prognosis associated with the establishment of the diagnosis of malignant melanoma. However, while these advances were being made, a considerable number of variations in the approach to the problem have been suggested.

Extremes of Therapy

All of us remember the small pigmented lesion that was burned off by a dermatologist "never to recur," which ultimately destroyed the patient by wide-spread hematogenous dissemination. Thus one might say that cauterization of the local lesion is all that is necessary. Most of us, however, are similarly aware of the more common satellitosis that develops under these circumstances (Fig. 1).

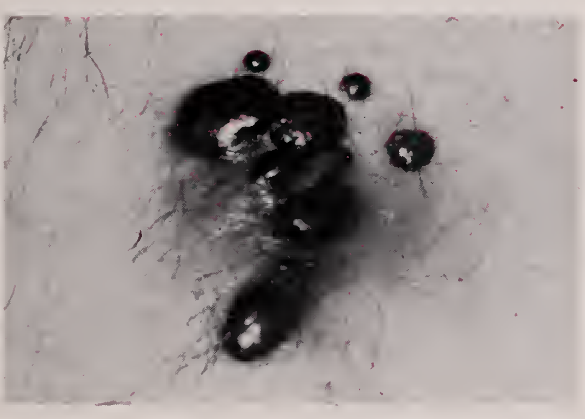

Fig. 1 — Multiple satellite nodules developing in the cutaneous and subcutaneous tissues around a primary malignant melanoma. This subcutaneous satellitosis is quite common in malignant melanoma and is the reason for demanding a much wider excision of the primary tumor than for many other lesions.

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*Department of Surgery, University of Illinois, College of Medicine, Chicago, Illinois.

At the opposite extreme, there is no question but what a forequarter amputation will control local disease when the primary tumor occurs on the terminal phalanx of the fifth finger. The routine application of such therapy, however, for a disease that primarily destroys the patient by hematogenous dissemination, seems to be an unnecessarily mutilating operation. It is hoped that a method of management somewhere between these two extremes can be evolved which will give the average patient the greatest chance of successful treatment.

Adequate or Inadequate Margin

The margin of excision adequate for the basal cell carcinoma or even for a squamous cell carcinoma of the skin is inadequate for malignant melanoma. Given a patient with a pigmented lesion which has undergone some recent change, however, does not necessarily immediately imply the necessity for wide local excision and skin graft. Such a procedure would resemble hitting a mosquito with a mallet. A simple local excision is all that is required until the diagnosis has been accurately established (Fig. 2). Occasionally one hears the argument: "Why not take a little extra margin so that you will be sure you are well around it?". But this will then leave the surgeon on the horns of a dilemma, should he find that the lesion he has removed is actually a malignant melanoma. He has done more than is necessary for the removal of a simple nevus, and yet he has not done enough for adequate local treatment of a malignant melanoma. The "little extra margin," however, is often quite tempting, and too often is relied upon as adequate. Nothing less than a two-centimeter margin of grossly normal-appearing tissue should be considered adequate for malignant melanoma. The initial simple excision should establish only the diagnosis. Additional treatment should begin when the accurate final diagnosis is established.

Biopsy Excision

The question naturally arises: "Is it ever reasonable to perform only a biopsy of the suspected malignant melanoma?". The rule of thumb which I employ is that if a diagnostic excision can be performed without creating a major cosmetic deformity or without requiring skin graft, such an excision should be undertaken. Under other circumstances, biopsy of the lesion, which can ultimately be incorporated in the subsequent definitive excision, seems a reasonable compromise (Fig. 3).

Maximum Salvage

In order to achieve maximum salvage, however, is there any advantage in additional surgical treatment beyond the adequate excision of the local primary tumor? The malignant melanoma can spread by both the lymphatic and the vascular systems. Since both spreads can occur and the sequence of their occurrence is unpredictable, many feel that an attack on the regional lymph nodes is unjustified until there is clinical evidence that the tumor has extended to this area.

Elective Node Dissection

Approximately ten years ago at the University of Illinois, discouraged by our limited success with therapeutic regional node dissections, we began to perform elective* regional node dissections for patients with malignant melanoma. If the primary tumor in the regional node group could be removed with a reasonable excision and dissection in continuity, this was considered the treatment of choice. Where the continuity was to be maintained, however, with only a few thin strands of subcutaneous tissue and fascia, a discontinuous operation was performed with a delay between the treatment of the primary tumor and the regional node dissection, varying from ten days to three weeks. In recent years the shorter period of time is the one generally employed.

Results of the Extended Treatment

In an effort to evaluate the effectiveness of the more extended treatment, the case records of 245 patients treated at the University of Illinois Research and Educational Hospitals and in private practice have been reviewed.[1] An over-all summary of this review is presented in Table 1.

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*The term "elective" is preferred to "prophylactic" when referring to a dissection of the regional lymph nodes clinically free of metastatic tumor. The dissection prevents disease as implied in the latter term only when tumor cells are present in the nodes. Such a situation exists in a minority of cases.

Palliative Treatment

Of the total, fifty-three patients were considered incurable either because of local extent of the disease, because of dissemination, or because the patient refused treatment. Seven of these patients had only a biopsy of the lesion for microscopic confirmation and were preterminal. All are dead. Fourteen patients received palliative irradiation. All are dead. Of twenty-seven patients who had local palliative excisions, twenty-six are dead. The one exception had an axillary node removed which was positive for metastatic melanoma. The patient refused axillary dissection. Unexpectedly, he is still living without evidence of disease some twelve years later.

Definitive Treatment

There are thus 192 patients who are considered to have received definitive treatment of their tumor. Forty-five of these patients were treated less than five years ago, leaving 147 patients treated and followed over five years. Five of these patients are indeterminate in that they expired without clinical evidence of the disease in less than five years of unrelated causes. There are thus 142 patients in the determinate series. In this group, thirteen have been lost to follow-up. These patients are presumed dead of their disease, though some of them had no clinical evidence of tumor when last seen. One patient is living with disease, while seventy-five died of malignant melanoma. Fifty-three patients are living clinically free of disease at five years, or 37.4 per cent.

There was essentially an even distribution in the sex of the patients, with 128 females and 117 males. As far as site distribution was concerned, the head and neck area was the largest group in this series with the lower extremity close behind. No primary tumor could be demonstrated in seven patients. One of these, surprisingly, is living free of disease after four years. The presumed primary

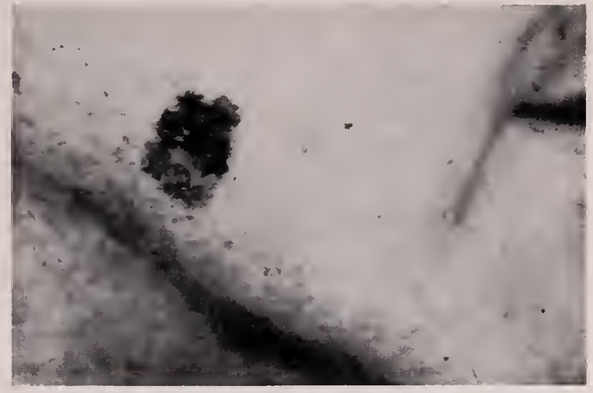

Fig. 2 — A pigmented lesion of the skin of the face which had recently undergone some enlargement. A simple diagnostic excision can be performed here without graft and this is the treatment of choice. When and if the diagnosis of malignant melanoma is established, the definitive management can then be undertaken.

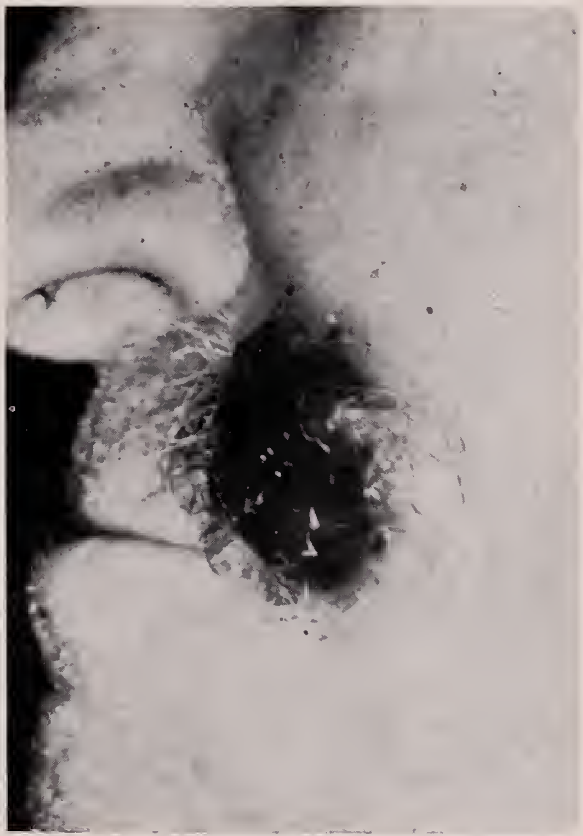

Fig. 3 — A large pigmented lesion of the upper lip at the commissure of the mouth. Even simple excision of a lesion of this size and in this anatomic position would require a major reconstructive effort. Under the circumstances, a biopsy of the lesion to establish the microscopic diagnosis is the treatment of choice. The extent of the subsequent excision required is thus established and proper definitive treatment and reconstruction can be carried out as a single procedure.

tumor in the lower leg was excised, followed by a therapeutic groin dissection; but subserial sections of the large pigmented lesion on the lower leg failed to demonstrate a malignant melanoma, but only an active junctional nevus.

Type of Treatment

The results of therapy varied considerably with the type of treatment employed.

Local Excision

In the 142 determinate patients, forty-two required only a local excision of the primary tumor and never developed clinical evidence of regional node disease. Sixteen or 38.2 per cent of these survived for five years free of disease.

TABLE 1
Malignant Melanoma
Total Experience

Total Patients		245
Palliative	53	
Treated Patients		192
Treated Less Than 5 Years	45	
5-Year Series		147
Indeterminate	5	
Determinate		142
Lost to Follow-up (Presumed Dead)	13	
Living With Disease	1	
Dead	75	
Living, N.E.D.*	53 (37.4%)	

*No Evidence of Disease Clinically

TABLE 2
Regional Nodes Clinically Negative at Initial Examination
Determinate Group

Treatment	Number	5 Years NED
Local Excision with and without Therapeutic Node Dissection	71	23 (32.4%)
Therapeutic Node Dissection	29	7 (17.5%)
Local Excision and Elective Node Dissection or Elective Excision and Dissection in Continuity	25	20 (80%)

TABLE 3
Head and Neck
End Results Determinate Group

Determinate Patients		38
Failures		
Postoperative deaths	2	
Dead of malignant melanoma	21	
Lost to follow-up	0	
Total failures		23
Successful Results		
No evidence of disease, 5 years		15 (39.5%)

Regional Node Dissection

Therapeutic regional node dissections were performed on seventy-five patients, either as part of the primary treatment or as subsequent therapy. Only seventen of these (22.6 per cent) survived for five years free of disease.

Elective Regional Node Dissection

Elective regional node dissections were performed on twenty-five patients, of whom twenty (80 per cent) survived for five years free of tumor. While this third group of elective dissections is considerably smaller than the other two, the improved increment of salvage is a statistically valid one.

Survival Correlation with Positive Nodes

The most obvious questions to raise at this point are: "How may patients who had a therapeutic node dissection actually had microscopic positive disease?"; "How many of the patients who had elective node dissection had similar microscopic findings?"; and further, "Is there a correlation between this and survival?". For purposes of evaluating this situation, a comparison of the patients who had no clinical evidence of regional node disease at the time of initial examination, but who had different forms of both primary and subsequent treatment, is in order (Table 2).

Local Excision

Of the seventy-one patients who had only a local excision as the primary treatment, twenty-nine (approximately 40 per cent) required a subsequent therapeutic node dissection. Twenty-six of these twenty-nine had microscopically positive regional node disease.

Therapeutic Node Dissection

It should be noted, however, that only seven of the patients who required a therapeutic regional node dissection and who had microscopically positive nodes survived (17.5 per cent). In other words, only seven of the twenty-nine therapeutic node dissections performed on patients who had originally clinically negative nodes were successful.

Elective Node Dissection

On the other hand, in our elective node dissection group of twenty-five, only four had microscopically positive disease. Three of these four are included in the twenty patients who survived five years without evidence of additional tumor.

At first glance, it would seem that with only four of twenty-five dissections microscopically positive in the elective group, and twenty-six of twenty-nine positive in the therapeutic group, there is no valid comparison between the two. It must be remembered, however, that all of the ninety-six patients at the time of their initial examination presented identical clinical pictures: a primary malignant melanoma with a clinically negative regional lymph node group. In those in whom the regional nodes were left untouched, 40 per cent subsequently required a regional node dissection, and a little better than 36 per cent actually had microscopic evidence of metastatic tumor. This is in contrast with the second group where only a small percentage had demonstrable metastatic disease on routine examination of the lymph node group. The difficulty in detecting small foci of metastatic disease on routine section of a regional node dissection has been well documented. Considering that these two groups were initially identical, it would seem very likely that better than 30 per cent of the elective node dissection group should have had metastatic tumor in the regional nodes if subserial section had been performed.

The Head and Neck Graft

Having concluded that an elective node dissection offered the optimum chance of survival for patients with malignant melanoma in general, a review of such lesions as occurred on the head and neck, which was the largest single group in this series, seemed in order. Traditionally, malignant melanoma of the head and neck has been considered a less aggressive tumor than such disease elsewhere in the body.[2] A brief but somewhat more detailed study of this particular classification, therefore, was in order.

Excluding oropharyngeal and orbital lesions from the original over-all survey, there were fifty-five patients to be evaluated with a malignant melanoma of the skin of the head and neck (Table 3). Thirty-eight of these fifty-five patients can be considered determinate and are the basis of this second study.[3] The cheek was the most common site of the primary tumor, and the prognosis in this group is somewhat above average (five to eleven). The scalp, the second most common site, had a below average survival, only two of nine. The poor prognosis in this group has been noted by others; the explanation may rest in the fact that since these primary tumors are not readily visible the lesion is more advanced when first noticed, as evidenced by a higher percentage of regional lymph node involvement in these patients when first examined.

The five-year end results of this determinate group showed fifteen patients (39.5 per cent) surviving free of disease. This result is essentially similar to that figure obtained in the over-all group and somewhat belies the statement that a tumor in this area is less aggressive than the disease in general.

Adequate Local Treatment

If the patients with melanoma of the head and neck are segregated in a manner similar to the one previously employed, there were twenty-one whose regional nodes were clinically negative at the time of initial examination. Only one patient whose initial treatment consisted of adequate local excision subsequently developed evidence of uncontrollable node metastases. The effectiveness of adequate local treatment in the head and neck area is further demonstrated by the observation that where a therapeutic neck dissection was performed with the primary tumor controlled, the five-year survival free of disease was 50 per cent. This is well above our over-all average.

In contrast with this group, where the primary was controlled, is the universally unsatisfactory result where the primary tumor recurred and there was in addition clinical evidence of regional node metastases. None of these patients survived. It should be noted that in no instance did a heroic attempt at salvage, either of the primary or metastatic tumor, produce either the salvage or significant palliation in this series.

Comments

The crux of treatment success of patients with malignant melanoma of the head and neck apparently is the ability to control the primary tumor. No patient who had a recurrent lesion and clinical evidence of regional node disease was without tumor for five years. On the other hand, four of nine patients with metastatic disease and control of the primary tumor survived. The prognosis for this group was not significantly different from that of those who had an elective neck dissection. With this as a background, it seems that malignant melanoma of the head and neck behaves somewhat differently from malignant melanoma in general; but the over-all prognosis is similar to the disease elsewhere. In the head and neck, adequate local control seems to be the major challenge. An elective neck dissection in this group of patients seems unnecessary.

In the treatment of malignant melanoma elsewhere, there is little doubt that an elective regional node dissection offers a distinct improvement in the over-all five-year salvage. Possibly our ability to detect clinical evidence of metastatic disease in the inguinal, iliac, and axillary areas is less acute than it is in the head and neck areas. This alone may account for the apparent discrepancy in survival rates. For whatever the reason, however, the performance of an adequate excision of the local lesion followed by an elective regional node dissection or an excision and dissection in continuity seems to offer the greatest chance of long-term survival in patients with malignant melanoma in areas other than the head and neck.

Summary

1. When a patient presents himself for treatment of a lesion which is suspect of malignant melanoma, the primary responsibility of the surgeon is to establish the diagnosis. This is done by a simple narrow excision of the lesion. Treatment of malignant melanoma does not begin until the diagnosis has been established, and compromises or extensions in the diagnostic procedure are unwarranted.

2. The performance of an elective regional node dissection ten days to two weeks following the adequate treatment of the primary tumor, or an excision and elective regional node dissection in continuity, offers the best prognosis for patients with malignant melanoma.

3. In the head and neck area, the performance of a regional node dissection may be deferred until there is clinical evidence of disease, if adequate treatment of the primary tumor is obtained.

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La Roque's Sign

Pressure over McBurney's point in gangrenous appendicitis may cause the right testicle to draw upward. As pressure is released the testis drops back to its usual position.

Idleness is the stupidity of the body, and stupidity is the idleness of the mind.
— Seume

Subcutaneous Emphysema

Complicating Bronchial Asthma in Children

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SUBCUTANEOUS EMPHYSEMA, always a complication of interstitial emphysema, is rare in children. Only 54 cases have been reported in the literature;[1-5] we are adding one more and briefly discussing this complication.

Report of a Case

An eight-year-old child became acutely ill on October 25th with severe coughing and labored breathing, after sustaining a bee sting of the hand 24 hours before.

Examination disclosed a pale, acutely-ill child who was having great difficulty exhaling. His nares were dilated and his chest was over-expanded. Faint breath sounds and wheezes were heard bilaterally. Crepitation was felt in the neck and in the lower jaws. Roentgenograms of the chest taken on admission revealed massive subcutaneous emphysema extending into both sides of the lower neck and left axilla. There was mediastinal emphysema, the heart being displaced posteriorly as a result of the air in the retrosternal space.

He was hospitalized and placed in an oxygen tent. He was given sixth-molar lactated Ringer's solution and 100 milligrams of hydrocortisone intravenously, and 1/10 cc. of adrenalin was administered every six hours subcutaneously. Within 24 hours he was moderately improved. However, he did not improve markedly until about four days after admission. On the seventh day X ray and palpation of the chest revealed no subcutaneous emphysema. He was, however, very fatigued, and when seen one week after this attack, still complained of being tired. The chest, however, was clear; and there was no subcutaneous emphysema felt in the neck or the face.

His mother informed us that when he was a small child it was his practice to step on bees and that he had sustained many bee stings. There was a family history of asthma. Since this attack he has had two episodes of asthma, triggered by changes in temperature and humidity. Skin tests were done and were positive for bee, hornet, and wasp stings.

Discussion

Pulmonary interstitial emphysema occurs when air escapes into the connective tissue septum from a ruptured alveolus.[1,6,7] The marginal type of pulmonary alveoli, whose bases lie against the connective tissue septa or on blood vessels, are the only alveoli concerned in the production of pulmonary interstitial emphysema. Rupture of partitional alveoli merely allows air to escape into other alveoli, whereas rupture of marginal alveoli allows air to enter the connective tissues surrounding either vessels or bronchioli. The air is forced along the sheaths of the pulmonary blood vessels to the hilums, then into the middle portion of the mediastinum along the pleural reflections of the pulmonary vessels. Dissection occurs between the potential areas of the parietal mediastinal pleura and parietal pericardium, and the air enters the anterior mediastinum and ascends along the great vessels to the neck and then out into the subcutaneous vessels. Subcutaneous emphysema is one of the sequelae of mediastinal

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emphysema and tends to decompress the mediastinal emphysema and to reduce cyanosis and dyspnea. Recent reviews have emphasized that asthma may lead to mediastinal emphysema by atelectasis with associated alveolar ectasia or increased intra-alveolar pressure resulting from forceful respiratory efforts against resistance, or may be due to some constitutional predisposition. Usually the condition is self-limiting and has a good prognosis.

Many patients respond to medical treatment, but other techniques have been reported. The two following cases illustrate successful results of other types of treatment.

Norman and Rizzolo described a 19-year-old male who complained of tightness and pain in the anterior chest after having undergone compression-pressure testing.[8] He had subcutaneous crepitation from the suprasternal notch throughout the anterior cervical region to the angles of both mandibles. A chest X ray showed air in the mediastinum with extension into the superior retrosternal area and neck. He was returned to the recompression chamber and became asymptomatic at six atmospheres of pressure.

McNicholl described the case of an eight-year-old male, asthmatic for four years, who was sensitive to dust, hay, mixed pollens, horse and cat dander. He developed marked dyspnea, cyanosis and subcutaneous emphysema above the clavicles extending to the axillae. Horizontal incisions were made 1½ inches above the clavicles, this tissue explored with forceps, and the air released.

Summary

A review of the literature discloses 54 cases of subcutaneous emphysema occurring in children. The condition is usually self-limiting and benign.

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Pliny's* Treatment for Headache

"The ashes of a burnt hare, mixed with oil of myrtle,** alleviate headache, the patient drinking some water that has been left in the trough after an ox or ass has been drinking there. The male organs of a fox, worn as an amulet, are productive, if we choose to believe it, of a similar effect; the same, too, with the ashes of a burnt deer's horn, applied with vinegar, rose oil, or oil of iris."

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*See Minnesota Med June 1964, Page 716.

**When turned out of Paradise, Adam took a grain of wheat and a sprig of myrtle — according to Arabian legend.

Evaluation of an Electric Sleep Device

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The induction of a sleep-like state through rhythmic and monotonous stimuli of low voltage direct currents has been investigated occasionally over many years. However, controlled studies for assessment of the element of "suggestibility" in this method have been lacking in the literature. This study tested a new pulsating current unit designed specifically for induction of relaxation and sleep. The results should be of interest to all practicing physicians.

PASSAGE OF an electric current through the brain has been proposed as a successful method for inducing bodily relaxation and sleep. During the past few years enthusiastic reports have appeared in Russian literature, based on studies performed with sophisticated electronic units that generate a current with specific, and supposedly favorable, characteristics. This is described as a pulsating current of rectangular shape with an impulse frequency of 5 to 25 cycles per second. The duration of impulse is constant within limits of 0.3-0.5 milliseconds and the milliamperes can be regulated individually for each procedure.[1] Utilizing padded electrodes over the eyes and mastoid processes Russian investigators have reported deep relaxation and sleep in their subjects when the current was adjusted below the level producing sensations of flickering lights. Abnormal sleep patterns were noted to improve.

The present study was designed to critically test an electric sleep device of Japanese design.** In an undated monograph Yutaka Mizushima[2] described favorable results using a similar device with repeated applications of short duration. Evaluation of his studies is difficult, however, since no control data are reported. Hence a controlled study was deemed advisable at this time.

Procedure

The aim of this study was to determine the effectiveness of a single, prolonged stimulation of the Japanese "sleep device" to produce sleep in various subjects, and further to determine the role and importance of suggestibility in the procedure. Wave characteristics were studied in the laboratory with an oscilloscope. The machine produces a rectangular wave of 19 cycles per second with an impulse duration of 1.3 milliseconds. Resistance between the leads was measured at 25,000 ohms when the electrodes were well saturated with saline solution. Current applied to the skin could be varied from 0.57 milliamperes (and 1.6 volts) to 1.8 milliamperes (and 5.2 volts) with a calibrated dial. The most commonly-used dial setting (for a current just below uncomfortable sensations in the patient) produced a current of 1.0 milliampere and 4.6 volts.

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**Manufactured by the Kawasaki Electric Industry Co., Ltd., Japan.

The study group consisted of 84 volunteers: 29 were members of the hospital house staff or medical students; 14 were members of the nursing staff; 20 were healthy post-partum patients; and the remainder were patients with various medical problems plus several of the hospital personnel.

We used three of the "electric sleep" machines, applied in the prescribed manner with electrodes consisting of cotton pads saturated with saline solution and fitted over the closed eyelids and the occiput of the skull, with the lead marked "negative" being attached to the eyelids and the lead marked "positive," to the occiput. The procedures were carried out with the subject in a comfortable, supine position on a bed in as quiet an area as practicable.

Although most of the subjects had some previous knowledge of the purpose of the apparatus, the procedure was explained briefly beforehand; also mention was made of the expected sensations of flickering lights and facial twitching. The current was then turned on and the dial turned up to the point where unpleasant sensations were experienced: for example, vibration in the teeth or twitching facial muscles. A test was not performed unless a "flickering light" sensation was apparent to the subject. The duration of the procedures varied from 30 minutes to two hours with a great majority lasting about 45 minutes. Each subject underwent only one procedure; each was checked verbally as to his (or her) status at approximately two minutes after turning on the current. At this point the dial was readjusted downward slightly or, if the subject was in the control group, the circuit was broken without the subject being aware of this maneuver.

Results

The test group as noted in Table 1 consisted of 46 subjects, 15 of whom experienced sleep, as evidenced by slow abdominal respirations and delayed arousal. Twenty-one of the test subjects experienced "deep relaxation," felt to be more prominent than one would have by simply lying quietly and comfortably for a period of time. The remaining six of the test group experienced no significant relaxation effect. Pulse, blood pressure and respirations were recorded on the first 12 subjects of the test group during and after the procedure, but as no significant change was found, this practice was discontinued. Blurring of vision for several minutes to one-half hour after removal of the electrodes was noted by all of the subjects. Visual acuity tests and funduscopic and slit lamp examinations were performed on three of the subjects immediately before and after the procedure, but no appreciable corneal or retinal change was noted. Due to blurring of vision, however a few subjects were ill at ease driving their cars after the test.

The control group consisted of 38 subjects. Of these seven slept, 21 experienced "deep

TABLE 1
Results of Testing Subjects With An Electric Sleep Device
(Current of 1.0 Milliampere and 4.6 Volts.)

Subject Response	Number of Subjects	Per Cent
Sleep Induced	15	32.4
Increased Relaxation	21	45.6
No Effect	10	22
Total	46	100%

TABLE 2
Results In Control Group Testing An Electric Sleep Device
(No Current Used)

Subject Response	Number of Subjects	Per Cent
Sleep Induced	7	18
Increased Relaxation	21	56
No Effect	10	26
Total	38	100%

relaxation," and the remaining 10 experienced no demonstrable relaxation effect. Those subjects in the test and control groups who experienced "deep relaxation" or sleep also noted other sensations during the procedure. Most had a shortening of time concept; many noted heaviness of limbs and numbness and tingling sensations in various parts of the body. A persistent feeling of relaxation "limpness" for varying periods of time after the procedure was noted by some of the test group. A few felt that this interfered with their physical and mental activity. No one complained of difficulty sleeping the night following the test. A few from both groups complained of transient headache.

Discussion

A comparison of results in Tables 1 and 2 reveals that 32.4% of subjects in the experimental group went to sleep when the current was used and 18% went to sleep with pads in place and no current flowing. This is the only significant difference in this study. Of the subjects claiming increased relaxation there were 45.6% in the experimental group (with current on) and 56% in the control group (with no current on). Twenty-two per cent of the experimental group and 26% of the control group reported no effect.

Apparently restful sleep was induced about twice as often when the current was flowing at the levels used in this study than when electrode pads were disconnected from the "sleep" unit. The similarity of results in the groups with "increased relaxation" and "no effect" would support a strong element of suggestibility in the use of this kind of device.

Summary

A study of the effect of a sleep device was performed. A total of 86 subjects was divided into test and control groups. The similarity of results shows that suggestibility plays a major role in the results obtained in the use of this particular sleep device.

Editor's Note: Other than as an investigative study, a sleep-inducing device cannot, at this time, be recommended for your insomniac patients.

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IT'S THE LAW
Consent To Treatment

A physician who administers treatment or performs an operation must obtain expressed or implied consent. If a person is injured and unconscious and his injuries require prompt attention, a physician who is called to attend him is justified in applying such treatment as is reasonably necessary for the preservation of life.

If, in the course of an operation to which the patient has consented, the physician discovers a condition which had not been anticipated prior to the operation, and which if not corrected would endanger the life or health of the patient, he is then justified in extending the operation to correct the defect.

A patient who has attained his majority and is of sound mind is presumptively qualified to give or withhold consent. The fact that a patient is being treated free or at the expense of someone else does not eliminate the necessity of obtaining his consent.

Stetler and Moritz: Doctor and Patient and the Law. C. V. Mosby Company.

Pneumoperitoneum

Interesting examples of clostridial infections are coming to light in increasing numbers. The advent of hyperbaric oxygenation has stimulated great interest in these problems. This kind of patient would be a likely candidate for therapy in a hyperbaric chamber at three atmospheres.

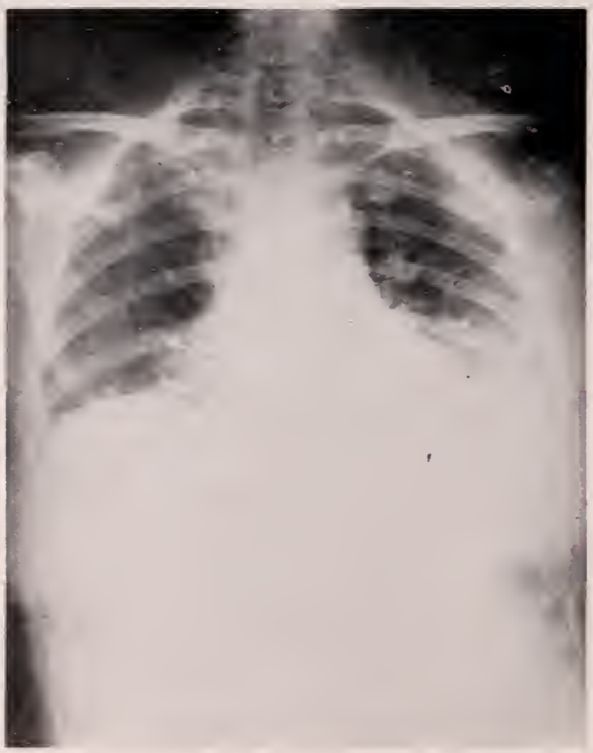

Fig. 1 — Upright roentgenogram of the chest eight days after enterolysis. Only a pleural effusion in the left hemithorax is present.

PNEUMOPERITONEUM MOST often follows abdominal operation, and is of no importance if promptly absorbed. Of pathological significance is pneumoperitoneum associated with perforation of a hollow viscus or with a fluid level in an intra-abdominal abscess. This report concerns a patient who postoperatively developed radiographic evidence of pneumoperitoneum produced by generalized peritonitis without rupture of a hollow viscus or intra-abdominal abscess. Review of the American literature fails to disclose a similar example.

Case Report

A 57-year-old white female was admitted to the University of Minnesota Hospitals on February 1, 1961. Eight days earlier at another hospital she had had an enterolysis, and during the operation had received 1500 milliliters of whole blood. Six days postoperatively, her urinary output was noted to be

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Due to Generalized Peritonitis Caused by Gas Forming Organisms

"markedly diminished" and she was transferred to the University Hospitals with a diagnosis of acute postoperative renal failure.

Physical examination on admission revealed a stuporous woman with Cheyne-Stokes' respirations. The blood pressure was 140/70, pulse 74, and temperature 97.6° F. A grade III systolic murmur was present at the left sternal border. The abdomen was slightly distended but not tender, the bowel sounds were high pitched, and rebound tenderness was absent.

The hemoglobin was 10.9 grams per 100 milliliters and the white blood cell count was 7,150 per cubic millimeter. Blood urea nitrogen was 189 milligrams per 100 milliliters; serum sodium, 120 milliequivalents per liter; chloride, 73 milliequivalents per liter; carbon dioxide combining power, 21 milliequivalents per liter; and potassium, 7.8 milliequivalents per liter. Direct and indirect Coombs tests were negative. An upright roentgenogram of the chest revealed a small pleural effusion in the left costophrenic angle but no pneumoperitoneum (Figure 1); a roentgenogram of the abdomen disclosed distention of the small intestine and colon.

A rapid intravenous infusion of 1000 milliliters of five per cent dextrose in water resulted in a urine volume of only 120 milliliters with a specific gravity of 1.014 during the first eight hours after admission. Obstruction of the urinary tract was ruled out by ureteral catheterization. The patient therefore underwent hemodialysis for six hours on the Kolff Twin Coil artificial kidney. For five days thereafter she was satisfactorily maintained on

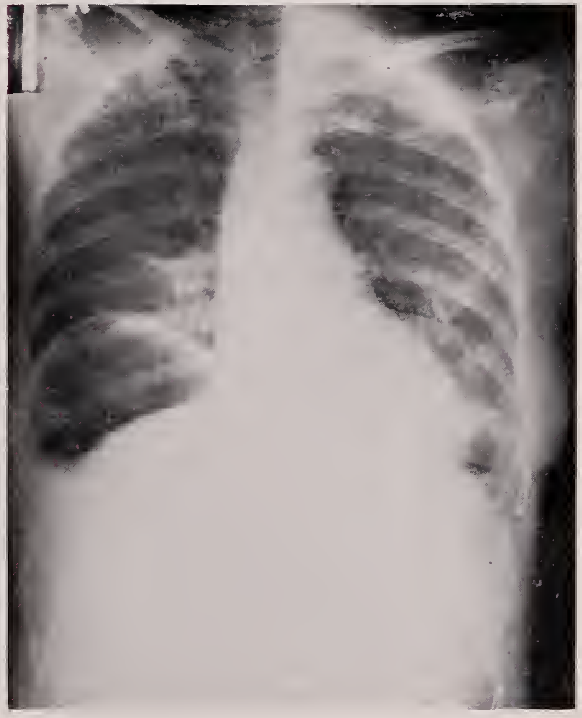

Fig. 2 — Upright roentgenogram of the chest sixteen days after enterolysis. Free air indicative of pneumoperitoneum is present under the right leaf of the diaphragm.

nasogastric suction and restricted intravenous fluids. On the sixth hospital day the blood urea nitrogen was 172 milligrams per 100 milliliters and another hemodialysis was performed. The patient remained afebrile and appeared improved. The nasogastric tube was removed and restricted oral fluids were allowed.

On the seventh day mild abdominal distention recurred and the temperature was 100.4° F. The following day the temperature was 101° F, and distention progressed despite nasogastric suction. The white blood cell count was 19,400 per cubic millimeter and an upright roentgenogram of the chest revealed massive pneumoperitoneum (Figure 2).

With a diagnosis of rupture of a hollow viscus, a coeliotomy was performed. On incising the peritoneum, foul smelling gas was released with a hiss, and the abdominal distention relented. Examination of the peritoneal cavity and its contents revealed 3500 milliliters of foul smelling serosanguineous fluid. Loops of bowel were covered by a shaggy fibrinous exudate, but no perforation of the gastrointestinal tract was found. A culture of the peritoneal fluid revealed many colonies of Escherichia coli and Clostridial species; blood culture drawn during operation was sterile. After copious lavage of the peritoneal cavity with saline, the operation was terminated. Achromycin 500 milligrams and aqueous penicillin 1,000,000 units were given intravenously every six hours thereafter, but the temperature remained above 102° F. until death, two days after operation.

Autopsy disclosed 2500 milliliters of purulent peritoneal fluid; there was no perforation of a hollow viscus. The kidneys were pale and swollen, and microscopical examination showed severe hydropic degeneration of the tubules. Post-mortem blood culture revealed an Escherichia coli bacteremia.

Discussion

Falkenburg[1] in 1913 described two patients who postoperatively developed progressive abdominal distention and who, on subsequent exploration, were found to have pneumoperitoneum without perforation of a hollow viscus. Upon incising the peritoneum, gas escaped with a loud hiss. Additional patients were described by Fründ[2] in 1914 and Stegemann,[3] who in 1923 named the condition gas peritonitis. In none of these four patients was bacteriologic study done.

More recently patients with gas peritonitis following operations for cholecystitis and intestinal obstruction were described by Adams[4] and Rhodes.[5] The pneumoperitoneum with peritonitis was not diagnosed prior to operation or autopsy. In these patients various Clostridia were found on bacteriologic study. In our patient culture of the peritoneal fluid yielded Escherichia coli and Clostridia, both of which produce gas.

These bacteria were often found in patients having peritonitis without pneumoperitoneum,[6] and we can offer no explanation for the pneumoperitoneum in our patient. Aside from slight abdominal distention interpreted as ileus on roentgen examination, no evidence of peritonitis was evident on admission. She remained afebrile until the seventh day after admission to our hospital, 15 days postoperatively. The following day pneumoperitoneum and leukocytosis were observed for the first time. In retrospect, whereas abdominal paracentesis would have aided in the diagnosis of gas peritonitis, exploration was indicated because of the possibility of a rupture of a hollow viscus.

Summary

In a patient who postoperatively developed generalized peritonitis with pneumoperitoneum (gas peritonitis) bacteriologic study of the peritoneal fluid revealed Escherichia coli and Clostridial organisms, both of which produce gas. Roentgen examination and abdominal paracentesis should be useful in diagnosis. Operation should not be delayed, since rupture of a hollow viscus must be excluded.

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The law of success: more bone in the back and less in the head. — Jacob Braude's "Speaker's Encyclopedia"

Bronchial Surgery*

WILSON WEISEL, M.D.**
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DURING THE past 15 years there has been a liberal application of laboratory methods to the treatment of abnormalities in the vascular and bronchial systems. An appraisal of the results of these treatments in the vascular field has been prominent in the surgical literature of the past few years and is continuing. We believe that the field of bronchial surgery has reached an age of maturity and can be subject to careful appraisal. This evaluation is not only indicated but necessary. It is with the intention of utilizing a retrospective approach in the examination of some newer surgical methods of treatment of bronchial disease that this paper is undertaken.

The role of the bronchial and respiratory system in the maintenance of body homeostasis has been well demonstrated and its function shown to be essentially that of a specialized conduit for alveolar ventilation. It is a two-way artery which contains and conveys a low viscosity vehicle and exhibits a reactivity similar to other components of the vascular system.

Foremost among the contributors to the field have been Gebauer, Paulson and Shaw, Langston, Bjork, Kiriluk and Merendino, as well as many other workers.[1-15] Illustrative of the patients who have benefited from this application of laboratory techniques in the clinical field is the following case report.

Case Report

A 32-year-old white male was admitted to the hospital in January 1952. He had been involved in an auto accident 42 days previously, at which time he had had a fracture of the femur in addition to a serious thoracic injury. The fact that his right bronchus had been torn from the trachea was evident at the time of his bronchoscopy, although this portion of his injury had previously not been recognized (Figure 1). The patient was prepared for thoracotomy by appropriate measures and this was performed 46 days after his accident.

At the time of surgery a clotted hemothorax was evacuated from the right chest, and the right lung was decorticated. After establishing the fact that the pulmonary artery and veins were intact, the

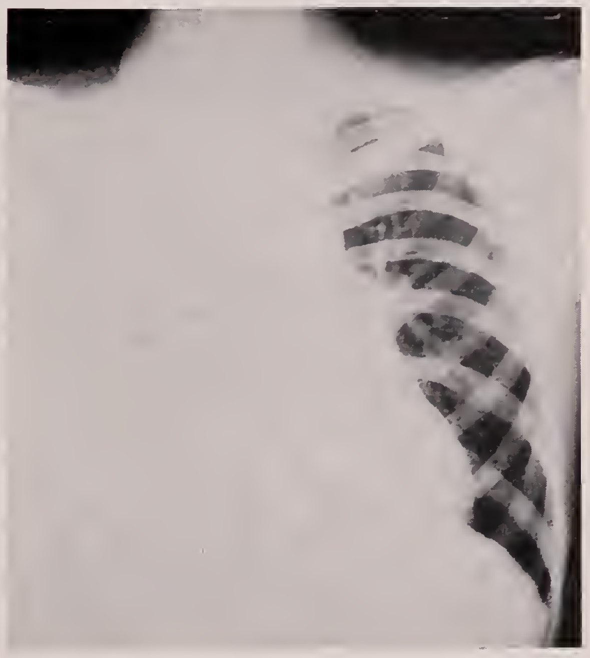

Fig. 1 — Posteroanterior X ray of chest showing opacification of right thorax.

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*Delivered at Northwestern Medical Association Meeting, February 18, 1964.

**Clinical Professor of Surgery, Chairman, Department of Thoracic-Cardiovascular Surgery, Division of Surgery, Marquette University, School of Medicine.

right bronchus was isolated and the distal end transected and debrided, and a bronchial cast of mucilaginous material removed. The lung was inflated, and anastomosis of the right bronchus to a new window cut in the trachea was accomplished. The patient's convalescence was satisfactory.

Evaluatory studies five years after surgery showed a relatively normal appearing X ray of the chest; and lung volume studies, as well as split lung functions, determined that more than 50% of the ventilation was carried out by the right lung and 52% of the oxygen uptake conducted by the side. Similar findings were observed when the patient was examined 10 years following his surgery, at which time bronchoscopic studies showed an essentially normal right bronchus with no evidence of bronchostenosis at the site of his new anastomosis. X-ray studies and pulmonary function tests performed 12 years after his bronchial anastomosis have been normal (Figure 2).

This patient, then, demonstrates the efficacy of the application of bronchial anastomosis to relieve bronchial obstruction and to restore bronchial continuity even in a patient who has had an atelectic lung for 46 days. Not only is the procedure of bronchial anastomosis effective, but the presence of bronchial obstruction and lung collapse per se does not mean that irreversible changes in the alveolocapillary function will necessarily result.

In addition to the traumatic and postinflammatory lesions, the situations which have lent themselves most admirably to the newer techniques in bronchial surgery from the standpoint of operative methods and the likelihood of long-term follow-up results have been in the realm of so-called benign bronchial tumors. In considering these lesions we are not referring to the pathologic classification or evaluation of the tumor but rather to a group of abnormalities in which clinical experience has proven treatment-principles for preservation of lung substance and for restoration of functioning pulmonary parenchyma to be effective for selected patients.

The following case reports demonstrate utilization of some of the newer techniques of bronchial surgery.

Case Report

A 30-year-old white male was admitted to the hospital on September 24, 1954, because of hemoptysis of three months' duration. Physical examination showed a well developed, well nourished, somewhat apprehensive male in no acute distress. There were no abnormal physical findings and the laboratory

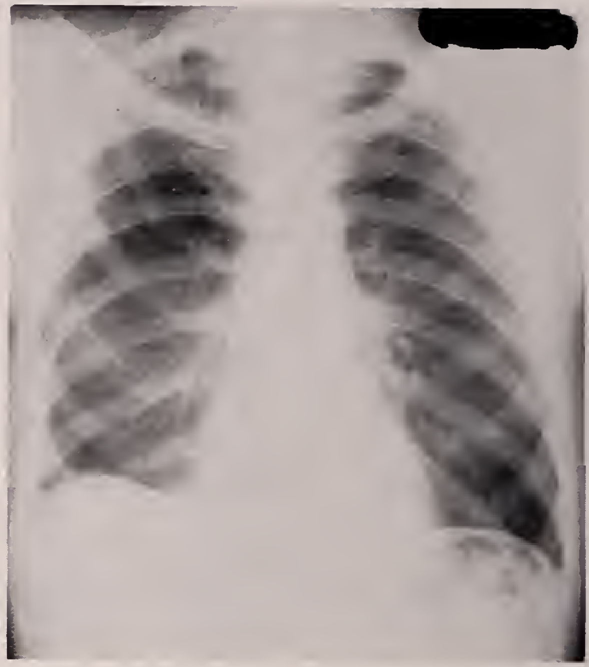

Fig. 2 — Postoperative roentgenogram made 12 years after right bronchial anastomosis.

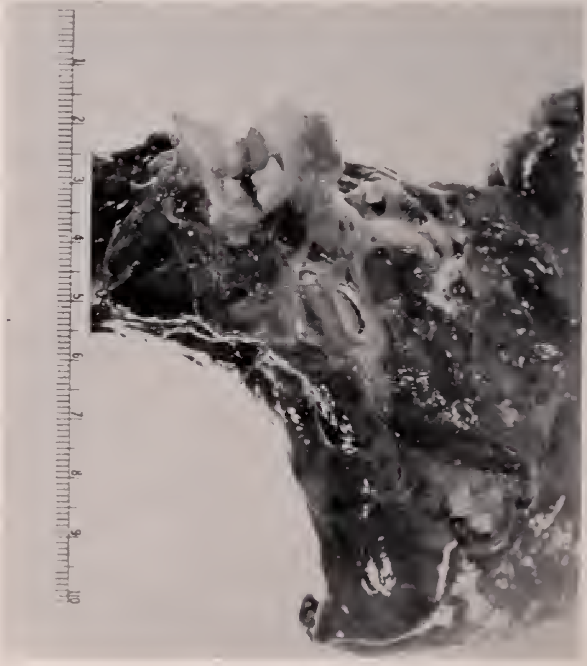

Fig. 3 — Gross specimen of right upper lobe and right main bronchus containing the carcinoid tumor.

findings including thoracic roentgenograms were within normal limits. At bronchoscopy, a tumor mass obstructing the right upper lobe bronchial orifice was seen, which proved to be a carcinoid type of adenoma (Grade I Adenocarcinoma).

At right thoracotomy the right upper lobe along with the right bronchus from the trachea to the right lower and middle lobe orifices were resected (Figure 3). The trachea was closed, and the right lower lobe bronchus was anastomosed to a new window placed in the lower portion of the right lateral trachea. Pathologic diagnosis on bronchial biopsy was confirmed by examination of the surgically removed specimen. The patient's convalescence was uneventful. In the follow-up of this patient, bronchoscopy and pulmonary function studies were performed at three-month intervals for one year and annually for an additional five years. The patient has been working, has been completely asymptomatic, and has exhibited a normal roentgenogram for the past 10 years. Pulmonary function studies performed 10 years following his bronchial anastomosis have been within normal limits, and split lung functions have shown that approximately 40% of the oxygen uptake is carried out by the remaining right lung.

This patient demonstrates the feasibility of bronchial resection and anastomosis in the preservation of normally functioning parenchyma, as well as the efficacy of limited resection in this type of tumor.

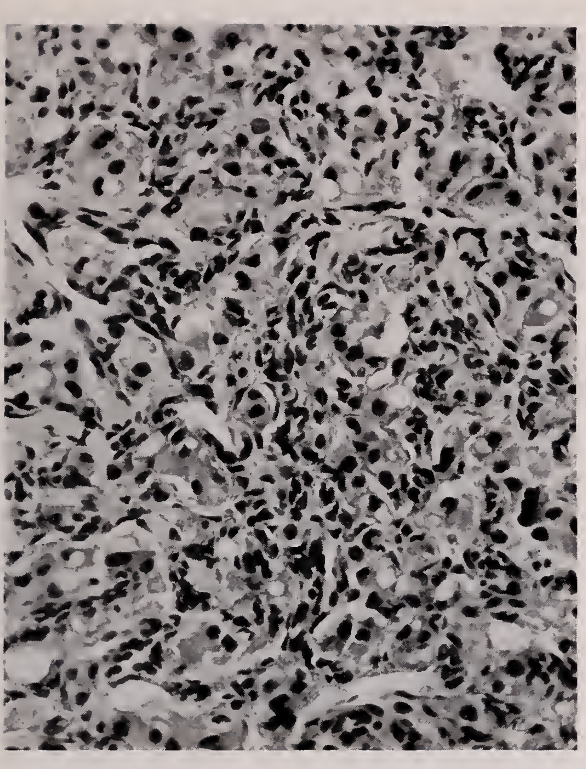

Fig. 4 — Photomicrograph (x 100) demonstrating the anastomosing cords of cells making up the tracheal carcinoid adenoma.

Case Report

A 17-year-old white female student was admitted to the hospital September 10, 1959, because of wheezing and a cough of four years' duration. At the age of 13 this patient's symptomatology had begun, and she had been actively treated for asthma during this time with no amelioration. During the previous two years the patient had noted progressive shortness of breath and occasional hemoptysis. X rays of the chest were within normal limits, but a bronchoscopy showed a tumor mass filling the trachea in its lower third.

At thoracotomy the tumor-bearing portion of the trachea about one inch above the carina was resected, involving an area of two inches of the lower third of the trachea. The lesion proved to be a carcinoid type of bronchial adenoma (Grade II Adenocarcinoma) (Figure 4).

Tracheal reconstruction was performed with a pedicled pericardial graft in tubular form. Follow-up bronchoscopic studies were performed at three-month intervals for one year and annually for the next four years (Figure 5). This patient has been well and has led a most active life completely free of symptoms since her surgery.

This case demonstrates the application of an autogenous graft of pericardium for replacement of a circumferential defect of the trachea, and follow-up studies have shown the complete efficacy of this procedure.

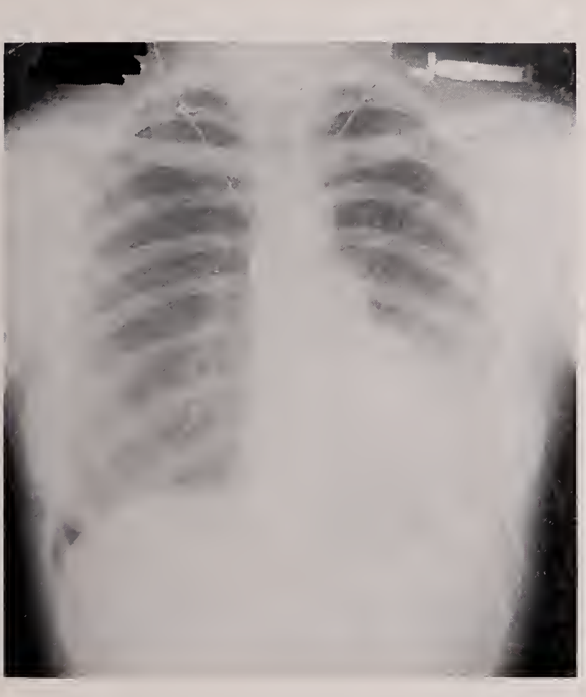

Fig. 5 — Postoperative thoracic roentgenogram four years after replacement of circumferential segment of trachea by the pericardial graft.

Case Report

A 17-year-old white male was admitted to the hospital on January 11, 1961, with a chief complaint of hemoptysis of two months' duration. Physical examination was within normal limits and thoracic roentgenograms were considered negative. Bronchoscopy demonstrated a tumor of the right upper lobe bronchus that could be seen with the right angle telescope and was confirmed by bronchographic studies. At right thoracotomy the right upper lobe bronchus containing the tumor was resected. The three segmental bronchial divisions of the upper lobe, i.e., apical, posterior and anterior, were formed into a single cylinder by 5-0 cotton sutures. This cylinder structure was then utilized as a single bronchus and reanastomosed to the previous take-off location of the right upper lobe bronchus. The postoperative course of this patient was satisfactory, and follow-up examinations including bronchoscopies, X rays, and pulmonary function studies have shown a return to normal of all of his studies, including a complete re-expansion of the right upper lobe (Figure 6). The patient is active and has recently successfully completed his boot training for the Marine Corps.

This patient demonstrates the application of a new type of bronchial anastomosis developed in the laboratory as an experimental method of extension of techniques in bronchial surgery. We believe that with a cylinder type of anastomosis it is possible to successfully complete the refunctionalizaton of small units of the bronchial system to the larger parts of the same system with increased effectiveness.

Comments

The primary physiologic derangement produced by all of these obstructing lesions that we have described is interference with the normal flow of air in the bronchial tree with the resultant pathologic effect on the lung, depending upon the degree of obstruction and the size of the bronchus or respiratory segment affected. The physiologic impact of these lesions can be demonstrated by various means, but one of the very simple clinical tests that can be utilized and is particularly noteworthy when larger bronchi are involved is that of the single breath spirogram. When the spirographic tracings of these patients are compared to those of the normal individual the slowing of the flow rate and the increased residual air becomes most evident.

Conclusions

Although the number of patients presenting the type of benign bronchial lesions we have described are not frequent, the surgical treatment of these lesions and the efficacy of an approach to preserve functioning pulmonary parenchyma can be effective. It is hoped that the successful results which we have reported in this small group of patients and which have been demonstrated in a larger group will help point the way toward exten-

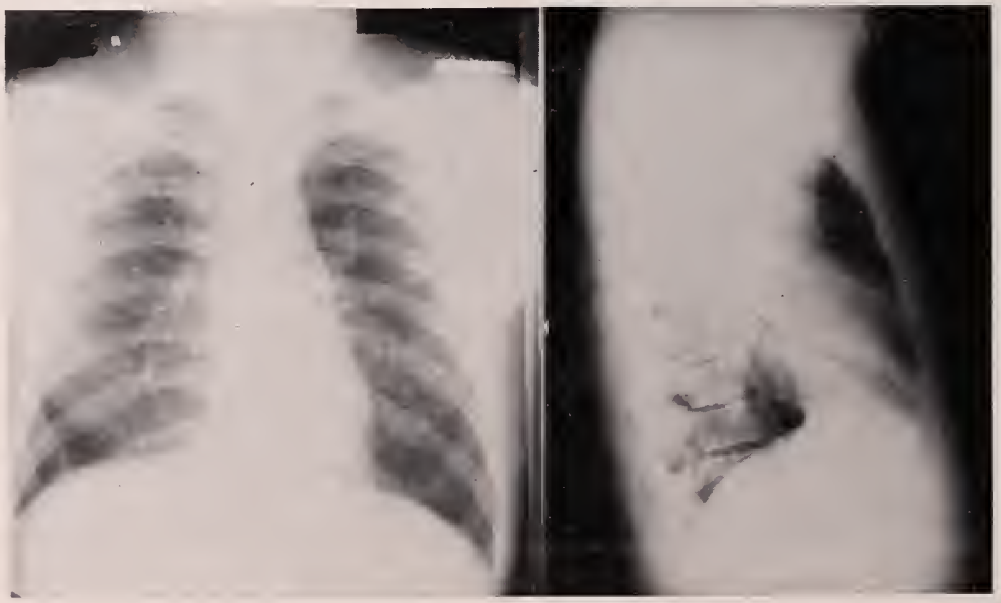

Fig. 6 — Postoperative X ray of chest one year following bronchial resection for carcinoid tumor and cylinder type of bronchial anastomosis.

sion of surgical operations for the correction of bronchial lesions of different types with increasing efficiency and greater numbers in the future.

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WHAT'S YOUR DIAGNOSIS?

Mrs. A. J., age 62, had previously had a heart attack and had been taking "some medicine for her blood." She was admitted to the hospital because of gastric bleeding and melena. There had been no history of ulcer. X-ray examination revealed no evidence of stomach or duodenal ulceration. The hemoglobin was found to be 9 grams and dropped to 6 grams within 24 hours. Repeated transfusions were then given but the hemoglobin could not be maintained during the next 48 hours. Therefore, an exploratory operation was done.

What's your Diagnosis? Turn to page 1369.

Cato and Cabbage

Cato, the dominant Roman for three generations, stood in the path of Greek learning. Cabbage was his panacea. He wrote: "Cabbage is good for everything." And this further: "keep the urine of one who is wont to eat cabbage. Warm it. Immerse the patient in it. You will soon cure him by this treatment. It has been tried. Also if you wash small children with this urine, they will never become weakly. And if there is any bruise it will break it up and heal it if you apply mashed cabbage. And if any ulcer or cancer arise in the breasts apply mashed cabbage, it will heal it."*

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*Massengill, Samuel E., M.D.: A Sketch of Medicine and Pharmacy, The S. E. Massengill Company, Bristol, Tenn.-Va., p. 19.

When Physick's dearly bought, it doth much healing bring, But when 'tis freely given, 'tis ne'er a useful thing. — *John of Mirfield (14th century)*

The Attitude of the Ancient Church Toward Medicine

Part II*

Paganism, not the Church, was responsible for the despisal and debasement of the physical aspect of man. Jesus saw man in his wholeness, both spirit and body. He stood in the tradition of Hebrew thought and life reaching back into the Old Testament with its belief that God is the Creator of man and the world in every aspect. "And God saw everything that he made and behold, it was good" (Genesis 1:31).

Gnosticism

The dualism between flesh and spirit which consigns man's physical well-being to the realm of insignificance or fatalism stems from a religious movement in late antiquity called Gnosticism, or in other forms, Manicheism. Gnosticism moved into the Roman Empire from unknown origins in the East about the same time as did early Christianity. It was one of the major religious movements of the time which in many places subverted and distorted Church teachings. Gnosticism promised salvation by release from bodily existence. In this life we are to repress or ignore the body, which is called "a stinking tomb."[3] Such doctrine is a far cry from that of Paul: "Do you not know that your body is a temple of the Holy Spirit within you, which you have from God?" (I Corinthians 6:19). In official pronouncements and the works of its best theologians the Church repeatedly rejected the errors of Gnosticism and rightly branded it a misleading faith. But as with many such errors its influence did not die with its condemnation. Gnosticism continued to have a subtle and distorting influence on much of Christendom for centuries to come. In 529 Justinian closed the medical schools of Athens and Alexandria at the promptings of Church men. In 1215 Innocent III condemned surgery. In 1248 dissection and the study of anatomy were pronounced sacrilegious.

Human Wholeness

Because of the dominant attitude in official Church circles the progress of scientific medicine came only in modern times with its separation from the Church.

Yet this tragic separation is not to mark the future developments of either medicine or religion in our culture. Modern medicine has made it apparent that the sick person presents to the physician not simply an isolated physical problem. Often the very cause and course of an illness are related to the mental, emotional and spiritual adjustment of the patient. Man must be viewed in his wholeness by the physician. No isolation of the physical from the spiritual reality of man is possible. Similarly, the religious message of today must recapture the concern for the wholeness of man so clearly seen in its Biblical origins, yet so often obscured in its history. The rediscovery of human wholeness involves both medicine and religion in a common crusade for man's welfare.

NOTES: All of these works are easily available and can help expand on the positions developed in this paper.

Donald G. Dawe, Th.D.
St. Paul, Minnesota

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*Part I appeared in Minnesota Medicine Oct. 1964, Page 1238.

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1. Dorfman, W., and Johnson, D.: *Overweight Is Curable*, New York, The Macmillan Company, 1948, p. 16.

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Editorials

Hyperbaric Oxygenation

A scientific article in this issue* of the journal presents an interesting patient with peritonitis due to a gas-forming organism. For many years we have de-emphasized this type of infection in our country, for reported cases have appeared sporadically and results of therapy have been disappointing.

The recent advent of hyperbaric oxygenation as a therapeutic approach in medicine has re-awakened interest in anaerobic infections of this kind. We now recognize that, for the first time in history, we have an ideal form of therapy which can be applied readily in the treatment of infections due to clostridium Welchii. Drenching of the body with oxygen quickly suppresses growth of these anaerobic organisms and patients improve clinically within a matter of hours. Interestingly, more cases of this type are now coming to light in most communities in the United States and infections of this type appear to be more prevalent than we had supposed.

Experience with hyperbaric chambers in Amsterdam and Glasgow, has demonstrated immediate improvement in critically ill patients with an improved state of well-being and freedom from fever within 24 hours after initial therapy. Customarily patients have been subjected to three atmospheres absolute pressure and have breathed 100 per cent oxygen through special fitting masks. Therapy has been continued for two hours and repeated twice daily for several days.

The recently completed hyperbaric oxygenation facility at the research laboratories of the Minneapolis Medical Research Foundation (at Hennepin County General Hospital) now provides this type of therapy for patients in the central northwest portion of the United States and southern Canada. Physicians may contact the Department of Surgery at the Hennepin County General Hospital, Minneapolis, Minnesota, in the event they have patients requiring treatment of this kind.

Claude R. Hitchcock, M.D., Ph.D.
Minneapolis, Minnesota

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*Doberneck, R. C. and Reiser, M. P.: Pneumoperitoneum Due to Generalized Peritonitis Caused by Gas Forming Organisms. Page 1344.

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Electroshock and Depression*

Electroshock is still a highly potent treatment for certain psychiatric illnesses. Formerly, it was considered obsolete by many psychiatrists; but recently, a renewed interest in electroshock has arisen because of waning enthusiasm for antidepressant drugs. Statistics on material treated exclusively with antidepressant drugs frequently show a fairly high percentage of improvement, but full recoveries as seen more commonly with electroconvulsive therapy are few.

The recent lack of enthusiasm for electroshock therapy resulted from the feeling that drug therapy was fashionable and that electroshock therapy was old-fashioned and barbarous. Further, the sales pressure generated by drug companies was enormous. Statements in the literature and drug company "throw-aways" to the effect that this or that drug resulted in improvement in 27% of patients with involutional melancholia, and 37% with manic-depressive psychosis, failed to mention the fact that electroshock therapy resulted in a 75% remission rate in the former group and 80% in the latter — in a shorter period of time and with less morbidity.

Electroshock should be used to treat the affective components of severe psychiatric illness, whether they be neurotic depressions, psychotic depressions, schizophrenic reactions, or manic-depressive reactions. It is also effective treatment for psychosomatic symptoms such as severe pain and anorexia,[2] which are indicative of severe affective states.

The advocates of drug therapy for affective states list fractures, memory loss, fear, and mortality as disadvantages of electroshock therapy. Today, with the correct use of muscle-relaxant drugs such as anectine, fractures are infrequent in electroshock therapy. In fact, most authorities[3] state that fractures are more common among patients taking antidepressant drugs than among those undergoing electroshock therapy. These drugs cause hypotension and syncope, resulting in injury and broken bones. Memory loss is not a complaint of patients who get good results with electroshock therapy; but it is bothersome in patients with neurotic depressions who do not respond well to electroshock therapy. This group, however, also does poorly with the antidepressant drugs; indeed, antidepressant drugs are associated in many patients with some memory loss and inability to concentrate.

The complaint of fearfulness in electroshock therapy is an insignificant one when handled by an understanding psychiatrist. Fearfulness also occurs among patients on antidepressant drugs.

Mortality from electroshock therapy is insignificant and should hardly be mentioned as a complication.

Antidepressant drugs have important disadvantages. Besides being less effective than electroshock therapy, they act too slowly, are expensive and toxic, and most important of all, are associated with suicidal attempts. Since some of these drugs have a two or three-week lag in their effect, suicide becomes a definite risk during this period besides resulting in a longer period of hospitalization and greater expense than if electroshock therapy were used. Severe toxic side-effects of many commonly used antidepressant drugs include jaundice, hypotension, intracranial hemorrhage, and death.

In summary, electroshock therapy is again considered the treatment of choice for affective components of severe psychiatric illnesses, especially in those affective illnesses that require psychiatric hospitalization.

Irving C. Bernstein, M.D.**
Minneapolis, Minnesota

Continued

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*Panel discussion, Minnesota District Branch of the American Psychiatric Association.

**Clinical Associate Professor, Psychiatry and Clinical Associate Professor, Obstetrics and Gynecology, University of Minnesota.

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Elective Induction of Labor

THE AUGUST issue contains the second report from the Worthington Clinic on the elective induction of labor, reflecting an experience in about 800 cases. Results as they concern maternal and fetal welfare presented by these conscientious and experienced obstetricians are unassailable from any point of view, and they emphasize the fact that the patients were beautifully selected according to the accepted rigid standards which should govern the elective induction of labor. Furthermore, the exercise of meticulous care in the conduct of the induction — meaning rupture of the membranes and the intravenous administration of oxytocic agents — is evident in the report. The reports of Schade and associates show that remarkable results can be obtained from elective induction of labor.

However, a dispassionate review of elective induction should include consideration of some negatory aspects of the procedure. In the first place, the very process of careful selection in itself provides normal obstetric subjects devoid of any actual or potential obstetric or medical complications, and thus the results in such a shielded category should be expected to be good. Second, in some of the other extensive reports on elective induction, it is shown that the risks of prematurity may be appreciable and that possibly the maternal risks may be increased as a consequence of trauma. Third, some serious accidents are known to have occurred, such as rupture of the uterus and damage to the fetus caused by poorly controlled use of oxytocic agents or maternal sensitivity to them. Freeman and Barno reported 25 maternal deaths associated with the use of oxytocic agents from the Minnesota Maternal Mortality Survey over a number of years, with preventable factors in most of the cases. But elective induction of labor did not play a major role in these cases, and the pituitary products had been given intramuscularly and injudiciously in most cases. Finally, failure of elective induction of labor in rare instances has required resort to cesarian section. Certainly, in view of the foregoing possibilities there is no place for the *unsupervised* medical induction of labor in either the general or specialty type of obstetric practice.

Convenience in itself (to patient or physician) may not be the best primary indication for the use of any medical or surgical procedure. Conversely, the inconvenience of some measure need not be sought out if obstetric risk can be avoided conveniently.

The environmental conditions in the study of the authors referred to above were such that the risks of elective induction of labor were either nil or minimal. But when such environmental factors as the constant presence of control by the physician are not available — a safeguard hardly possible in the practice of a busy general physician who must work alone — the elective induction of labor exposes the obstetric patient and her unborn child to indefensible risks. In one case of elective induction known to the writer all possible factors appeared to justify use of the measure (normal gravida III, para II, 43 weeks' gestation, condition of the cervix favorable, physician constantly available and so on). Yet the outcome was rupture of the uterus, fetal death and hysterectomy — surely distressing sequelae of an *elective* procedure.

The practice of quasi-indicated elective in-

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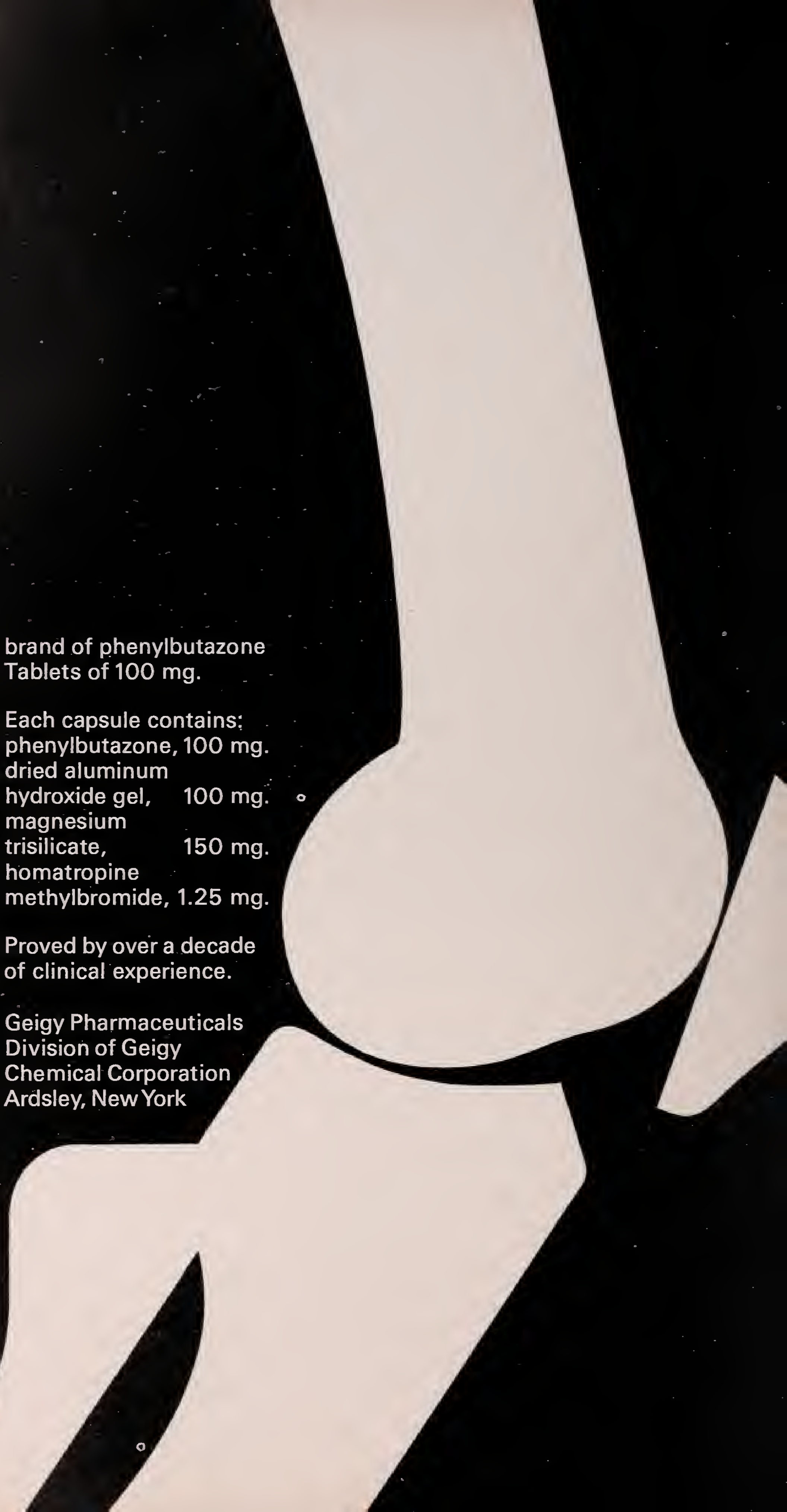

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duction can hardly be opposed if it is well conducted. Conditions are not the same for the patient who gives a history of rapid labor and who lives in the country 20 miles away from her hospital as they are for her pregnant sister who lives a block from the hospital.

The reports of the Worthington Clinic show that elective induction reduces the duration of labor by about 50 per cent in primiparous and multiparous women. This reduction probably is salutary, up to a point. Conversely, it is possible that too short a labor at times may be produced by elective induction. Physiologically, the uterus in labor has certain functions to perform by way of dilating and retracting the cervix and expelling the fetus. Too extensive a departure from the more leisurely natural process of spontaneously initiated labor and constriction of this process into too short a period may not prove to be an undiluted virtue.

The authors of the papers under consideration have shown that, with guiding effects of titration of the quantities of oxytocic agent during administration, the proper uterine contractions can be obtained in a sizable number of cases. Others, less alert or less skillful, or those who delegate this procedure to paramedical personnel, at times are confronted with tumultuous uterine contractions. When this untoward complication is at hand the strain is so intense that something must yield, and it may be the uterus, or the cervix (lacerations), or the fetal brain may be the victim.

D'Esopo, Moore and Lenzi recently have reported that women in induced labor "showed more rapid labors and what are interpreted to be the effects of such labors, which include cervical lacerations, post-partum hemorrhage, and depressed infants." However, these writers feel that the rapid labors were the results of cervices already in a state of dilatation for parturition, rather than of the induction itself. In fact, they, in common with Schade and others, believe that women who thus face rapid labor can be better managed by elective induction.

In conclusion, those who can select their patients expertly and conscientiously and personally can conduct carefully controlled elective induction in an ideal obstetric environment probably can do so with good results for all concerned. It is more likely, however, that most obstetricians and general practitioners will prefer to use elective induction only sparingly or when the measure is quasi indicated.

Arthur B. Hunt, M.D.
Rochester, Minnesota

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Bronchial Surgery

THE PRESERVATION of functioning lung tissue in young patients by means of various technics richly deserves the emphasis so well presented by Weisel.* The responsibility for preserving functioning lung tissue should be felt keenly by every thoracic surgeon. Though particularly true in the young patient with benign lesions, the task of preserving functioning lung in the older patient with malignant disease will arouse agonizing conflicts largely based on the prevailing philosophy that the patient's improved survival might

Continued

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*Weisel, Wilson: Bronchial Surgery. Page 1347.

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well be directly related to the extent of the resection. In good conscience, surgeons have extended the degree of resection of malignant lesions in the lungs in the hope of improving the less-than-gratifying results of the past. But the iatrogenic respiratory insufficiency imposed on some surviving patients having lung cancer may bring to mind an old cliché with respect to "something being worse than death." Evaluation of current results in surgical treatment of lung cancer suggests that, in certain cell types, less rather than more radical excision is indicated, even to the extent of utilizing technics of bronchial anastomosis. The late morbidity and mortality of radical pulmonary resection lend support to a surgical philosophy that permits the application of conservative technics and preservation of functioning lung in selected patients with lung cancer.

Philip E. Bernatz, M.D.
Rochester, Minnesota

The Editor's Soliloquy

Homo Sapiens — Are You in Trim?

In its original design the body of man was no doubt a thing of beauty, grace, and proportion; but Homo sapiens, despite his superior intelligence, has succeeded in making his body the most unsightly of all. A perfect human specimen is so rare that very few can qualify.

The elegantly-clad model, with her raw bones, countable ribs, and protruding spinous processes like the skeleton of a dinosaur, is not a body to admire; nor does the luxuriously-clad and girdled matron, with her stay-imprinted folds of skin, arouse admiration for the human form. Similarly, the male contours duplicate the unsightly anomalies of the female; both sexes, through ignorance, error, and abuse, are guilty of heresy to the most highly evolved structure nature has produced.

In his Song of Wild Laughter Jack Couffer, extolling the sure power and sleek litheness of a giant cat and the proud poise, grace, and agility of an antelope, declares man's body to be a "miserable thing." When one observes the exquisite hummingbird, the exotic tropical fish, the noble Arabian horse — three of nature's most superb creations — man seems almost reptilian in his doughy and knobby nudity.

Yet was man not made in God's image!

Carl O. Rice, M.D.

The body is but a pair of pincers set over a bellows and a stewpan and the whole fixed upon stilts. — Samuel Butler

I never thrust my nose into other men's porridge. It is no bread and butter of mine; every man for himself, and God for all of us.—Cervantes

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Curbstone Consultation

Overweight Patients

QUESTION: Would longevity be increased if a lifetime overweight patient were finally able to reduce to the desired weight at age 45? If so, how much?

ANSWER: With a few exceptions the mortality among the men who reduced their weight is appreciably less than in the corresponding weight-height classifications for which these overweights were rated. For example, among medium height men at issue ages 15-39 who at issue weighed 195-214 pounds, the mortality ratios after weight reduction are 113%, compared with 135% for those with or without minor impairments and weighing 195-214 pounds in the main study. At issue ages 40-69 the corresponding ratios are 108% and 128% respectively. The mortality of overweights who reduced is generally comparable with that of standard risks. In most classifications by age and duration the overweights who reduced show mortality ratios which do not exceed 100%, but in a few instances, notable for short men weighing 195-214 pounds at issue and for tall men 215-234 pounds, the mortality ratios are of the order of 125%.

In other words, from the above it is obvious that, as a group, individuals who reduce down to normal, or the standard according to their heights and weights and remain the same, have a substantial reduction of mortality.

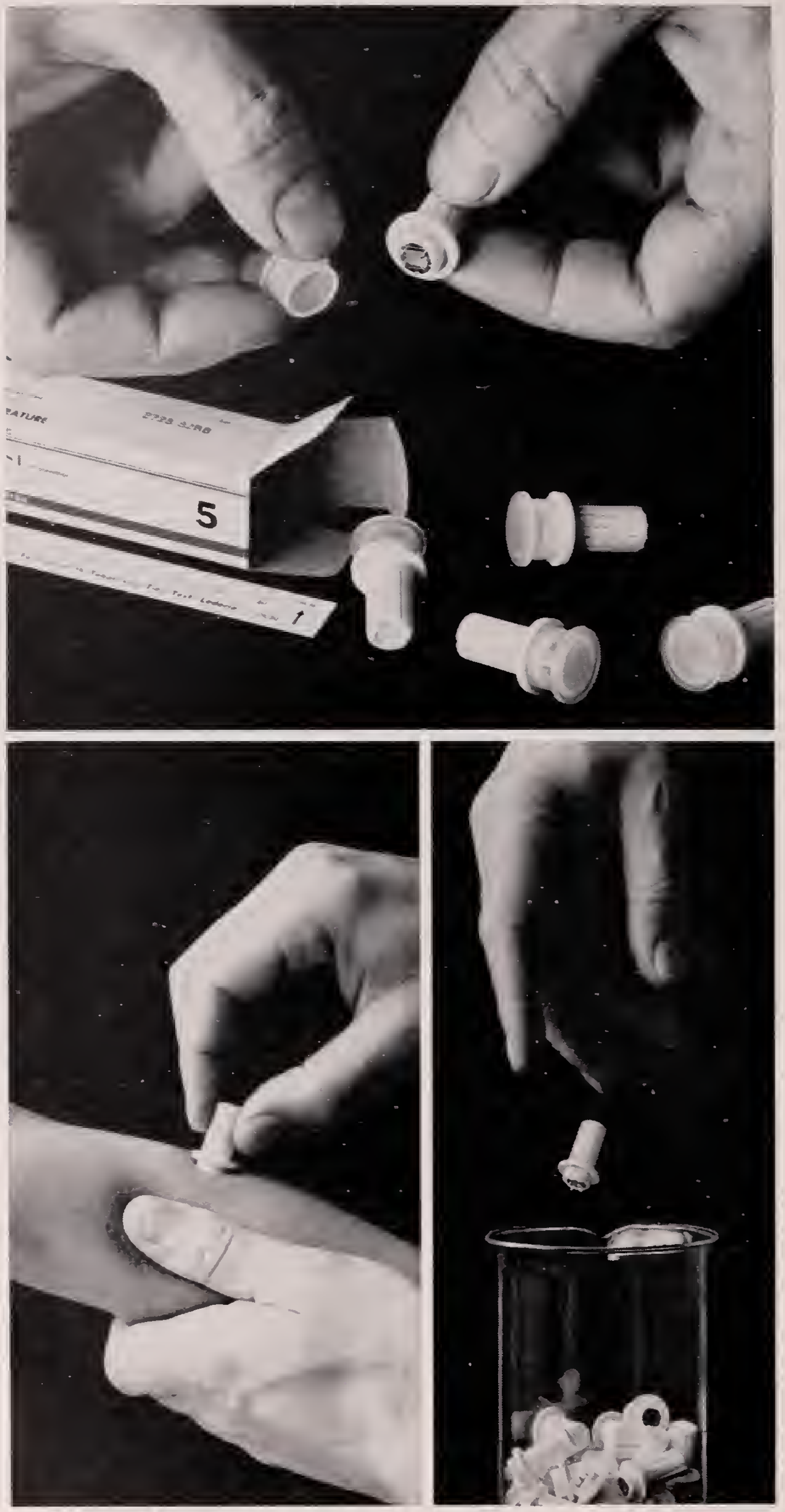
Karl Anderson, M.D.
Vice President,
Northwestern Life Insurance Co.

Interstitial Keratitis

QUESTION: Is penicillin the most effective treatment for interstitial keratitis as a manifestation of late congenital syphilis?

ANSWER: Generally interstitial keratitis will not respond to the penicillin therapy alone. A good response can usually be effected through the use of corticosteroids locally in the eyes, in addition to penicillin. Such a case should be managed in conjunction with the supervision of a competent ophthalmologist.

The measure of a man's real character is what he would do if he knew he would never be found out. — Macaulay



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Fracture–Trauma Conference

A Septic Hip?

A seven-week-old white male infant was admitted to the hospital for further evaluation and treatment of a possible septic right hip. The pertinent history included the fact that he had had diarrhea for one week prior to admission, but there was no history of other illness or injury. The parents had noted a reticence on the part of the baby to move his right leg for several days prior to admission, which became much more noticeable the day before admission when the family doctor was called and referred the child to a pediatrician. A presumptive diagnosis of septic hip was made and orthopedic consultation requested. There had been no fever noted.

On initial examination, the baby was found to be lying in bed quietly with the right hip in flexion, abduction and external rotation. The right thigh was obviously larger in circumference than the left and, in fact, measured seven and one half inches in circumference as compared to the left which measured seven inches. The baby was moving the left lower extremity but not the right. Passive motion of the right leg caused him to cry in obvious pain. There was increased warmth of the right thigh as compared to the left, but the baby was afebrile.

Admission laboratory work included a hemoglobin of 9.7 grams percent and a white count of 9700 with 38 per cent p.m.n.'s and 62 per cent lymphocytes. The urinalysis was negative; the sedimentation rate was 11 mm. per hour. A blood culture was drawn.

Admission X rays of the pelvis in the anteroposterior and frogleg projections were done and are shown in Figure 1.

Suspecting the diagnosis of a septic process, the right hip was aspirated anteriorly with negative results. The question of arthrotomy for drainage and culture arose. A decision to temporize was made, and the right leg was placed in three pounds of Buck's traction.

The following day it was noted that the right knee jerk was less active than the left. Initially, both knee jerks had been active and equal. In addition, there was now found to be bilateral ankle clonus of 10 to 15 beats, which had not been present when the child was first seen in the pediatrician's office. The sensation in both lower extremities was apparently nor-

Continued

mal. The child did withdraw both lower extremities from pinprick to the sole, but the right reaction was lethargic and the left active. Because the significance of the neurological findings was questionable, consultation was obtained.

A neurologist saw the child on the day following admission, and it was his opinion that the decreased motor activity in the right lower extremity was secondary to a "local muscular involvement" rather than neurological disease. A repeat set of X rays of the pelvis with the hips in the neutral and frogleg positions was done as well as X rays of the entire spine in the anteroposterior and lateral projections. The pelvic X rays are shown in Figure 2. They were interpreted to be negative as were those of the spine.

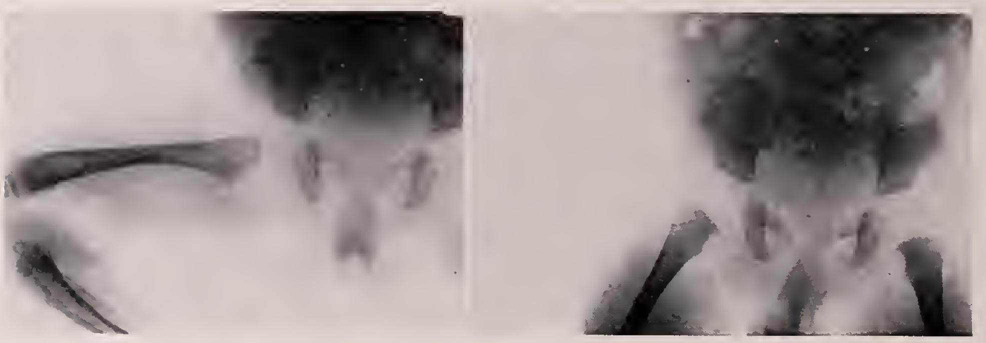


Fig. 1 — Initial anteroposterior and frogleg anteroposterior projections.

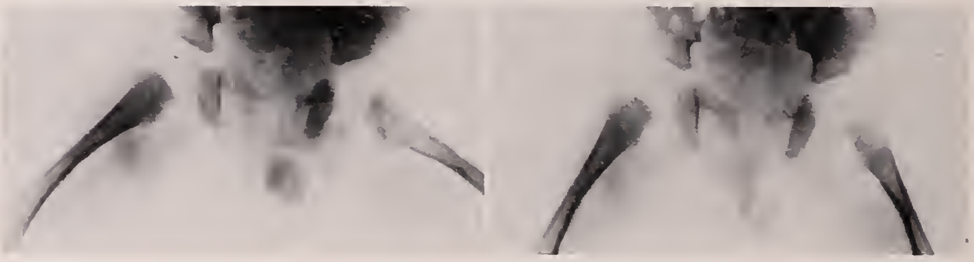


Fig. 2 — Anteroposterior and frogleg anteroposterior projections taken the day following admission.

Two days following admission, the right hip was again aspirated from the anterior aspect with negative results. During the following three-day period, the child remained afebrile. A repeat white blood count was 11,300 with 22 per cent p.m.n.'s and 72 per cent lymphocytes. The sedimentation rate was 21 mm. per hour. At 48 hours, the blood culture was reported as showing no growth.

Five days following admission, the baby spiked a fever to 101 degrees (rectally). For the first time, a defined mass in the mid right thigh was palpable. This mass was firm, tender, and seemingly fixed to the deep tissue or bone. Osteomyelitis, bone tumor, or soft tissue tumor were suspected. X rays of the right hip and femur were obtained and are shown in Figure 3.

The diagnosis of spiral fracture of the right femoral shaft having been made, the child was placed in a right single hip spica and discharged the following day. The fever was felt to be a response to the hemorrhage and probable recent displacement of the spiral fracture. The baby was febrile only the one day.

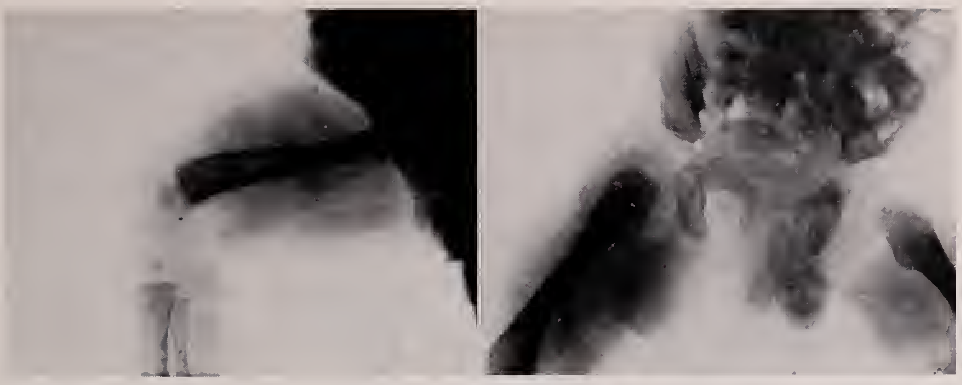


Fig. 3 — X rays of the right hip and right femur taken five days following admission. Diagnosis of fractured femur finally made.

Discussion

The problem of differentiating a fractured femoral shaft from a septic hip is usually not so great a problem as in this case. However, in spite of two sets of X rays in the anteroposterior and frogleg lateral positions, the fracture was not recognizable.

Usually, an infant with a swollen thigh, held in flexion, external rotation, and abduction, is a candidate for immediate arthrotomy of the hip if the X rays are negative for other pathology. Infants of this age need not show a white count response or a temperature elevation in the presence of a septic process. In this particular case, intuition apparently prevailed, and the child was spared a surgical procedure.

The point should be emphasized that multiple X ray projections and follow-up films must be done to rule out definitely a fracture when another diagnosis cannot be made with certainty.

Frederick E. Drill, M.D.
Minneapolis, Minnesota

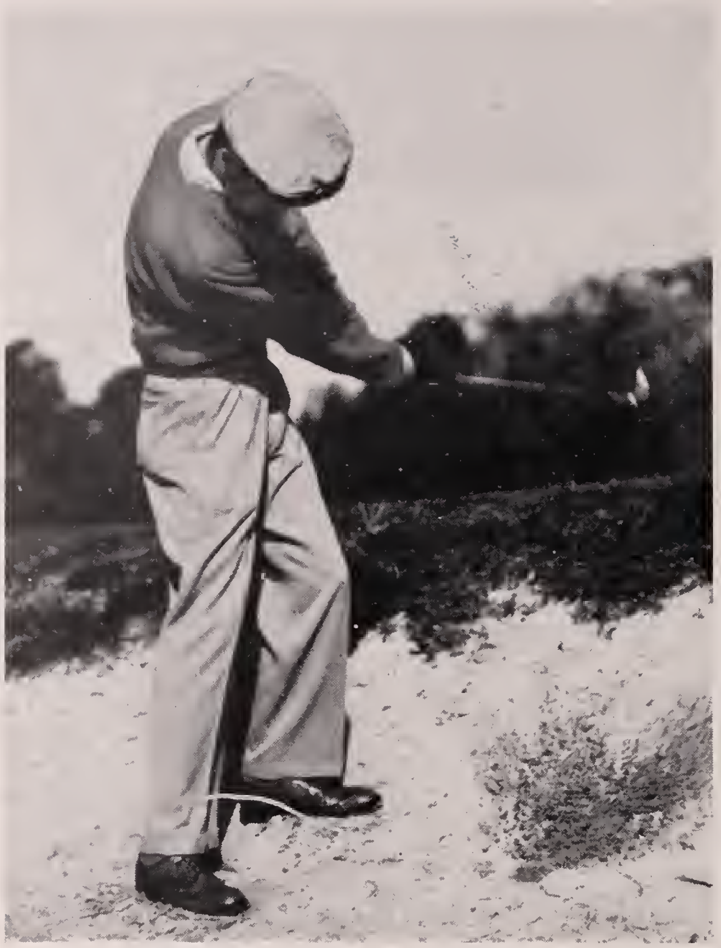
ANSWER TO WHAT'S YOUR DIAGNOSIS

(From page 1351)

At operation there was an area in the small gut extending a distance of 30 inches, showing bluish discoloration in patchy areas within the wall of the gut. Massive intraluminal melena could be seen within the gut and could be wiped away but the patches in the wall of the gut could not be displaced. In addition, there was a considerable amount of swelling and ecchymosis in the mesentery of the gut extending throughout a large portion of the mesenteric folds.

It was finally decided that no resection or further operative procedure be done, but that the patient should be given Vitamin K. Prothombin time was found to be 22 — control 12. Vitamin K was given. The following day the Prothombin time had dropped to 15- control 12 and no further bleeding occurred. The patient made a satisfactory recovery. The medication for her blood had been dicumerol.

I will be agreeable. I will look as well as I can; dress becomingly; talk low; act very courteously; criticize not one bit; not find fault with anything, and not try to improve or regulate anybody but myself. — *Flying High, August 1964*



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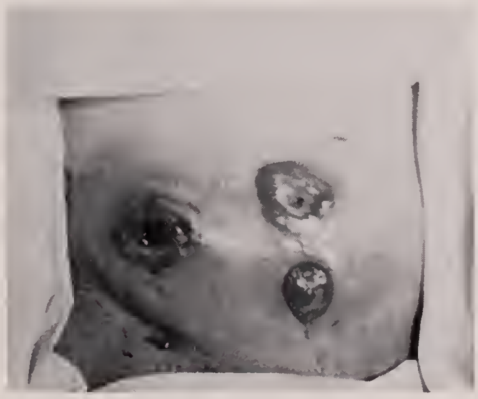
Tumor Conference

An Unusual Carcinoma of the Cecum

A 69-year-old man was transferred to the Minneapolis General Hospital from another hospital on January 10, 1953, with the admitting diagnosis of chronic postoperative incisional abscess. The history revealed that on July 22, 1952, he had been operated on for a ruptured appendix with localized peritonitis and abscess formation. The appendix had been removed with considerable difficulty. A perforation of the cecum was produced, but this was closed. A stab wound had been made lateral to the rectus incision for drainage. He developed an infection in the wound which opened and drained, causing a sinus in two places. In December 1952 because of persistent drainage from the stab wound and two areas in the incision, with a phlegmonous involvement of the abdominal wall, penicillin, streptomycin, and aureomycin were administered systemically without benefit. Tryptar irrigations locally did not promote healing. The patient ran a temperature from 99° to 101° daily.

On his admission to Minneapolis General Hospital there were three large granulomatous, draining sinuses in the right lower quadrant of the abdomen, surrounded by a hard, red, raised mass measuring 14 x 14 cm.



Preoperative sinuses

Laboratory studies revealed a hemoglobin ranging from 11.3 to 12.7 gm. The white count was 15,000 with a normal differential. The stools were positive for occult blood.

Continued

The colon X-ray study suggested a polypoid mass in the region of the cecum with a soft tissue tumor surrounding it. The roentgenologist was suspicious of an infiltrating polypoid carcinoma of the cecum, but in view of the previous surgery the possibility of an extrinsic process could not be excluded. The gastrointestinal spot films showed the terminal ileum to be displaced upward and medially by a mass which apparently surrounded the cecum, and an extrinsic inflammatory mass was the preferred diagnosis. A lipiodal study of the sinuses showed no communication with the bowel. Bacterial cultures of the sinus drainage showed proteus, staphlococcus aureus (coagulase positive), and gram-negative and positive rods. The culture for fungi was negative. A curettement of the sinus tracts in the abdominal wall was done, and section of the tissue showed a papillary adenocarcinoma.

Conference discussion ruled out the possibility of actinomycosis and tuberculosis, therefore it was recommended that an exploratory operation be done in an effort to determine the vesectability of the local lesion.

On January 28, 1953, exploratory laparotomy through a left oblique abdominal incision revealed that there were no palpable metastases in the liver, periaortic nodes, or mesentery. The mass was found to infiltrate the abdominal wall over a large area of the right lower quadrant of the abdomen. The fingers could be passed between the mass and the iliac vessels, and it appeared that this mass could be resected if a large area of the abdominal wall around the lesion could also be included in the resection.

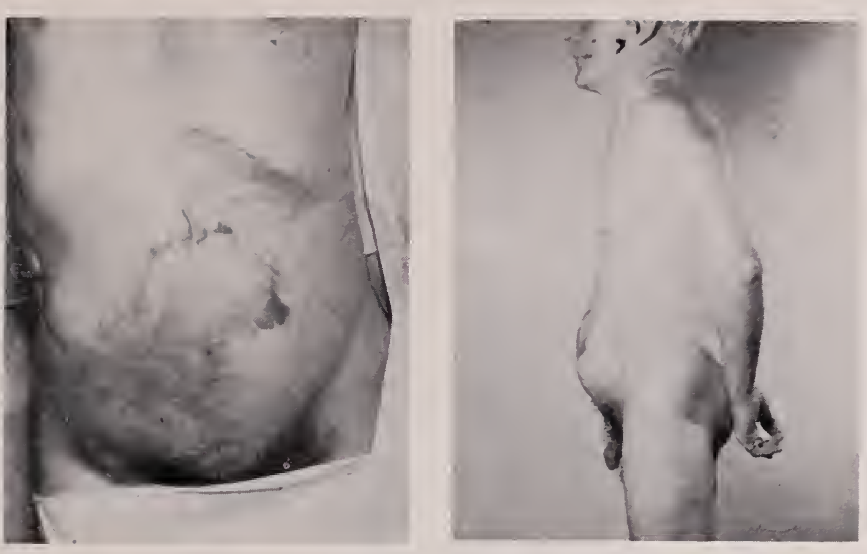
The incision was extended into normal tissue around the mass, and the mass was removed from the medial to the lateral side including all layers of the abdominal wall, an adherent loop of distal ileum, a portion of the urinary bladder, the right half of the colon and its mesentery. The right ureter was not involved. The opening in the bladder was closed and the end of the ileum was anastomosed to the end of the transverse colon. The abdomen was closed by swinging a skin flap from the left upper quadrant to the right lower quadrant. The donor site was covered by a free split-thickness skin graft from the thigh.

The patient's postoperative convalescence was uneventful except for the problem of wound healing, which was finally completed by using split-thickness graft on three separate occasions, for a period of about seven months.

The pathologic report indicated that the tumor mass had infiltrated the abdominal wall and that it measured 14 x 11 x 13 cm. The central portion was necrotic and hemorrhagic, and the peripheral portion firm and white. Microscopic diagnosis of the lesion was carcinoma of the cecum. Microscopic sections from the edge of the resected abdominal wall, the area attached to the urinary bladder, the lymph nodes from the greater omentum and from the curvature of the stomach, and a lymph node from the femoral canal region revealed no evidence of carcinomatous extension.

Comments

Although the skin flap became necrotic and required subsequent removal, is served as a good temporary covering for the bowel until fibrous tissue and granulation tissue had formed. The split-thickness skin graft on three separate occasions provided complete healing. The patient now wears an



Postoperative results

abdominal support for the ventral hernia. Periodic examination in the outpatient department during the past eleven years shows him to be in good health without evidence of recurrence.

In analyzing this case, several interesting features appear: (1) When operating for appendicitis the surgeon occasionally encounters a carcinoma of the cecum; he must recognize the pathology and institute proper treatment in order to avoid serious complications. (2) Although the carcinoma had locally infiltrated a wide area of abdominal wall, and at first the prognosis seemed very poor, a wide resection was of definite value and has enabled the patient to live in good health for eleven years. Locally extensive carcinoma of the colon without obvious metastases may well respond to radical attempts at salvage. (3) A quadrant of all layers of the abdominal wall can be removed and the bowel covered with a skin flap, though this type of closure presents problems in wound healing. This might be improved by some other measure of plastic closure. (4) With only skin and fibrous tissue covering the abdominal defect, the ventral hernia has not increased in size during the past eleven years.

Donald C. MacKinnon, M.D.
Malcolm M. McCampbell, M.D.
Minneapolis, Minnesota

When they come downstairs from their Ivory Towers, Idealists are apt to walk straight into the gutter. — Logan Smith

There's a divinity that shapes our ends
Rough-hew them how we will.—Shakespeare

I shall try to correct errors where shown to be errors, and I shall adopt new views as fast as they shall appear to be true views.—Abraham Lincoln

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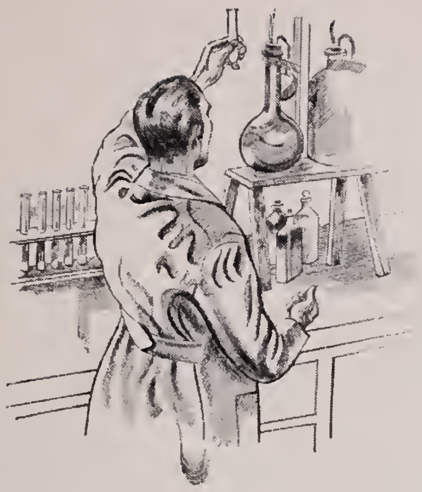

Clinical Path Conference

A Patient with a Bleeding Tendency

A 48-year-old farmer's wife was admitted to St. Marys Hospital with a three-year history of abnormal bleeding. This had started with severe menorrhagia and had been treated with transfusions and dilatation and curettage four months later. The menstrual loss had decreased slightly after this treatment, but spontaneous ecchymoses appeared on her trunk and limbs. About a year before admission, she had been given two pints of blood for menorrhagia and was treated at this time with vitamin K, with no apparent improvement, however. An attempt to control the menstrual flow by hormonal therapy was unsuccessful. Six months before admission, the patient's entire body, including her trunk, limbs, and face, had been covered with bruises. Treatment with vitamin K at another medical center was again unsuccessful. One month before admission, she had a large subcutaneous hemorrhage that extended from the right knee to the ankle. Three weeks later, she had a two-day episode of severe headache that began abruptly and gradually subsided. A few days before admission, there was some indication of disorientation and deterioration of memory.

Physical Findings

Physical examination revealed an obese patient, five feet seven inches tall, weighing 222 pounds. Ecchymoses were numerous on her face and the dorsum of her hands, legs, and abdomen. Her blood pressure was 120 mm. Hg systolic and 60 mm. diastolic; her pulse was 112 per minute, and her temperature 99.2° F. A slight weakness of movement of the right toes was noted, and there was a suggestion that both the Brudzinski and Kernig signs were positive. The neurologist who examined her suspected that she had had a small cerebral hemorrhage but had recovered almost completely.

Laboratory Findings

The hemoglobin concentration was 9.5 gm. per 100 ml. of blood, and the erythrocyte count 4,010,000 per cubic millimeter. The leukocyte count was 7100 per cubic millimeter with 29.0 per cent lymphocytes, 10.0 per cent

Continued

monocytes, 60.0 per cent neutrophils, and 1.0 per cent basophils. Urinalysis showed grade 1 sugar, grade 3 erythrocytes, and grade 1 pus. A special blood smear revealed mild hypochromasia with moderate anisocytosis and polychromasia; the platelets were abundant. Two determinations for blood sugar were 183 and 178 mg. per 100 ml., and the blood urea was 42 mg. per 100 ml. The results of serum protein electrophoresis were normal. Roentgenograms of the chest and skull showed no abnormalities. The whole-blood coagulation time was eight minutes, and the prothrombin time 80 seconds. Platelets totaled 261,000, and the bleeding time was four minutes. The coagulation problem was investigated further.

Discussion

It is evident from the history that this patient had a significant bleeding tendency that was manifested mainly by menorrhagia and ecchymoses. These types of bleeding can be seen in vascular, platelet, and coagulation factor abnormalities and are not very helpful in characterizing the problem any further. No mention is made of petechiae, which would be more indicative of platelet or vascular deficiencies.

The laboratory investigations showed a hypochromic anemia, which can reasonably be attributed to the patient's menorrhagia. The platelet count was 261,000, and, since platelets were noted to be abundant on the peripheral blood smear, thrombocytopenia probably was not a factor in this bleeding problem. The most striking abnormality in the coagulation studies was the prolongation of prothrombin time to 80 seconds.

The prothrombin time in the one-stage test (Quick method) consists of adding tissue thromboplastin and calcium to oxalated plasma and timing the formation of the clot. Tissue thromboplastin requires activation by labile factor (V), stable factor (VII), and Stuart factor (X), so that a deficiency of any of these cothromboplastic factors or a deficiency of prothrombin or fibrinogen may result in prolongation of the one-stage prothrombin time.

Congenital Deficiency

A congenital deficiency of all of these factors has been described in the literature, and, in situations of this type, there often is a family history of abnormal bleeding. This apparently is not present in this patient, however. In addition, it would be most unusual for bleeding of this severity to manifest itself for the first time when the patient was 45 years old, if bleeding was due to a congenital deficiency. On this basis, therefore, I think we can exclude a congenital coagulation factor deficiency as a cause of the bleeding.

Coagulation Factors

Thus, there remains for us to consider a group of acquired disorders that can result in prolongation of the one-stage prothrombin time. One can judge these disorders better if one remembers the pertinent physiology of some of the coagulation factors. Certain coagulation factors such as plasma thromboplastin component (IX), stable factor (VII), Stuart factor (X), and prothrombin (II) are produced in the liver and are dependent on vitamin K for their production. Vitamin K is a fat-soluble vitamin and is synthesized by the intestinal bacteria. Sterilization of the gut by antibiotic therapy may result in a deficiency of vitamin K, a consequent deficiency of the vitamin K-dependent clotting factors, and a prolongation on the one-stage prothrombin time. No history of antibiotic administration was elicited from this patient, but, in any case, it would be most unusual for the effects of such therapy to continue over a three-year period.

Biliary Disease

The diminution of the flow of bile to the gut in obstructive jaundice may result in malabsorption of the fat-soluble vitamins, but in this case the patient would have been jaundiced clinically. The various malabsorption syndromes also may result in deficient absorption of vitamin K, but there is nothing in the present situation to support the diagnosis of malabsorption. The patient was obese, and there was no history of steatorrhea. The hypochromic anemia, of course, can be seen also in malabsorption, but sufficient evidence is present to explain this on the basis of menorrhagia.

Disease of the liver may result in deficient production of the vitamin K-dependent clotting factors, but there is little evidence to support liver disease in this patient. None of the clinical stigmata of liver disease was present, and the Bromsulphalein retention was normal. Value for blood sugar was elevated, but the possibility of hemochromatosis in a menstruating woman with hypochromic anemia and without a palpable liver can, I think, be excluded.

Lupus Erythematosus

Some of the circulating anticoagulants seen in systemic lupus erythematosus may cause prolongation of the prothrombin time. In my experience, however, it has been unusual for these patients to have significant hemorrhagic phenomena. In fact, some have had thrombosing tendencies despite circulating anticoagulants. There is certainly nothing in the history to indicate systemic lupus erythematosus, although this possibility should be considered.

Anticoagulant Drug

Perhaps the commonest of the acquired bleeding problems results from the administration of anticoagulant drugs. The commonly used oral anticoagulants such as coumarin and indanedione derivatives cause a deficiency of the vitamin K-dependent clotting factors. Occasionally, one sees patients with psychiatric problems who administer these drugs to themselves, analogous to the patients who give themselves insulin to produce symptoms of hypoglycemia. These patients are nearly always women, quite often nurses, and they may have an antecedent history of thrombophlebitis. Although there was no history of thrombophlebitis in this case, I think that self-administration of one of the anticoagulant drugs must be strongly considered. I note that the patient is a farmer's wife, and since warfarin is commonly used as a rat poison on the farm, the possibility that this patient is ingesting warfarin must also be considered.

Doctor E. J. Walter Bowie

Coagulation studies showed that, in addition to prolongation of the prothrombin time, plasma clotting time was significantly lengthened, being

Continued

211 and 215 seconds (normal range 75 to 100 seconds). The prolonged prothrombin and plasma clotting times were both corrected by the addition of aged plasma. There was no correction using fresh barium sulfate-treated plasma. The Stypven time was normal, suggesting no significant depression of factor X. The thromboplastin generation test showed a striking coagulation deficiency in the patient's serum, whereas the patient's barium sulfate-treated plasma reacted normally. It was concluded from the coagulation survey that the patient had a deficiency of plasma thromboplastin component (IX) and stable factor (VII). The coagulation patterns described are seen most commonly when coumarin or indanedione drugs are administered and are strongly suggestive of this possibility. A spectrophotometric analysis of the patient's plasma confirmed the presence of warfarin sodium in the plasma, and it was found later that the patient had a bottle of warfarin sodium (Coumadin) in her possession.

E. J. Walter Bowie, B.M., B.Ch.*
Rochester, Minnesota

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*Section of Medicine, Mayo Clinic and Mayo Foundation.

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He that outlives a wife whom he has long loved, sees himself disjoined from the only mind that has the same hopes, and fears, and interests; from the only companion with whom he has shared much good and evil; and with whom he could set his mind at liberty to retrace the past or anticipate the future.—Samuel Johnson

Children should show more discretion in the selection of their ancestors. — Oliver Wendell Holmes

Don't put too fine a point to your wit for fear it should get blunted.—Cervantes

Neuro-Pediatrics Conference

Friedreich's Ataxia*

Dr. Daniel Murphy**

An eleven year-old white female presented with the chief complaint of poor memory and difficulty with balance for the past eight years. She was the third of seven children and the product of a full-term uncomplicated pregnancy; she was considered to be normal until the age of two, when she was involved in an accident in which a car backed over her and she sustained a pelvic fracture. At age four she fell and hit her head on cement steps, suffering a laceration over the right eye. At age six she fell from a second story window onto the lawn, fracturing her right collar bone. Skull films were not taken as there were no apparent neurological symptoms. The mother gave the history that the patient's gait was normal until the age of seven, when she began to have difficulty with her balance.

Besides this difficulty, her school work was consistently below average, though she had been allowed to pass from one grade to another, repeating only the first grade.

Physical examination revealed no significant abnormalities except neurologically. Mental-status examination showed her to be alert and cooperative, but she had difficulty in adding and a deficiency of information. Neurological examination showed bilateral absent knee and ankle reflexes and diminished bicep and tricep reflexes. Her plantar responses were extensor bilaterally. A positive Romberg and diminished ability to perceive vibration, motion and position sense were present. She had moderate difficulty with finger to nose test and a moderate intention tremor. There was no nystagmus. A mild pes cavus foot was noted with some weakness of dorsiflexion of the ankle. Some mild weakness of the extensors of the wrist was also present.

She was hospitalized at the University of Minnesota Hospitals, where psychometric testing revealed a fair amount of scatter on her scores; on the Wechsler Intelligence Scale for Children she scored 81 on the verbal and on performance, with an overall score of 85. However, her functional intelligence was probably even lower because of her neurological involve-

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*Sponsored by the U. S. Public Health Service Grant N2502A63. These conferences are an integral part of the Comprehensive Clinic Program at the University Hospitals. Co-ordinators for the project are Dr. Robert W. ten Bensel, in Pediatrics, and Dr. Robert Soll, in Adult Neurology.

**Senior medical student, University of Minnesota.

Continued

ment. Her other test scores in writing, spelling, and arithmetic showed her to be at the third and fourth grade levels. Spinal fluid examination showed one cell and a protein of 16 mgms. percent. The spinal fluid serology was negative. An electrocardiogram and an electromyogram with motor nerve conduction times were normal. An electroencephalogram was mildly abnormal, with some spiking in the left central region.

Dr. Ray Van Cleve* had given her routine child care, and at the age of two had treated her for a fractured pelvis, which occurred in a car accident. At that time, she had no residual abnormalities. In 1959, at the age of six, she was again evaluated, and no abnormalities were noticed except that she had difficulty with the finger to nose test. It had been four years since Dr. Van Cleve had last seen the patient, and the present recognition of her neurological problems was brought to his attention by Dr. Pearson, the school psychologist.

Dr. Van Cleve added further that this family seems to have numerous problems. The father has many anxieties and appears to be an unstable person, frequently visiting the doctor; the rest of the family, however, rarely come for medical attention. The mother appears to be a competent, stable person who does not vent her feelings outwardly. He felt that the family would need general support, particularly the mother.

Dr. Don Pearson** had performed a Stanford-Binet and a Wechsler Intelligence Scale for Children on which the patient scored an eighty-seven. He was particularly concerned about her "shakes," which had been noted by the teachers. He had also observed that there was an apparent emotional disturbance within the family, as they argued considerably, and some of the other children appeared to have emotional problems. The patient was given a battery of projective tests which showed her to be generally "anxious." Dr. Pearson felt that her awkwardness in writing and her gait disturbance may have been due to neurological disease.

Miss Francis Baxter*** described her "shakes" as a peculiar quivering of the hands and the position of the hands when writing. The child was also noted to have an unsteady-appearing gait which had led to some disturbance in her balance. From early in her school experiences she was felt to be "not normal." In the first grade, she had had some episodes of borrowing other peoples' belongings, and she had always been near the bottom of her class. She is now attending regular classes in the fifth grade, although not doing up to grade level. She is not difficult to deal with, and she strikes one's attention as she actively engages adults in conversation.

Dr. Michael Blaw† commented upon the neurological aspects of Friedreich's ataxia, the disease with which the child is afflicted. He pointed out that the main findings were characterized by involvement of posterior and lateral columns of the spinal cord.

Early Symptoms and Signs

Early symptoms and signs began in the legs with ataxic gait and pes cavus. Clumsiness of the hands, dysarthria and nystagmus develop later. Loss of reflexes may be an early sign, since the first involvement in the spinal cord is in the middle root zone, thus disrupting the reflex arc.

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*Physician, Austin, Minnesota.

**School Psychologist, Austin.

***Principal, Nevalin School, Austin.

†Pediatric Neurologist.

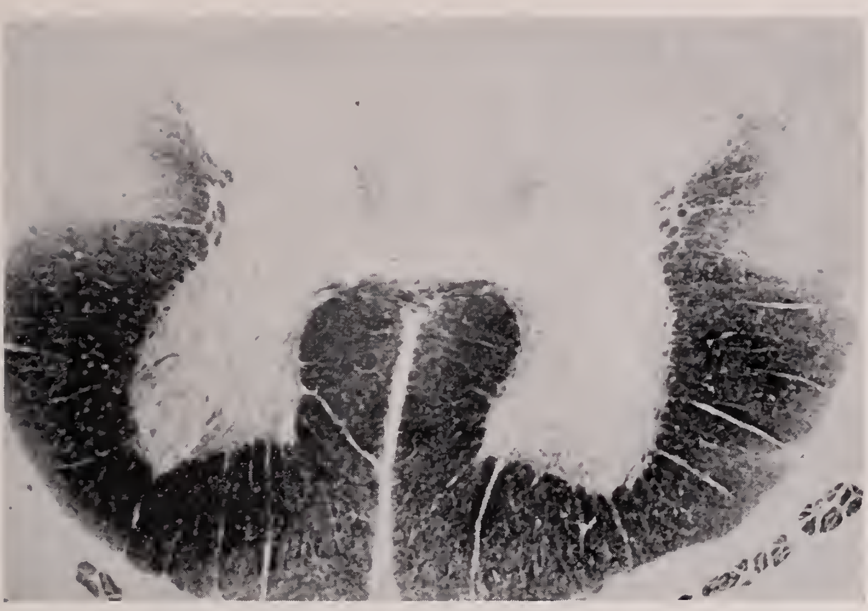

Fig. 1 — Lumbar section of spinal cord showing demyelination of dorsal and lateral column involvement as well as anterior horn cells and Clark's column in Friedreich's Ataxia. (Weil stain)

Pathologically, there is demyelination and very dense gliosis in the posterior columns throughout the entire length of the spinal cord. (Figure 1.) The anterolateral white matter in the region of the pyramidal tracts is also affected. The gliosis is very often intense and replaces atrophied fibers within the spinal cord. At times, there may be changes in the cerebellum with degeneration in the Purkinje cells.

Etiology

Dr. Blaw pointed out that although the disease is still unknown and there is no specific treatment, it is still extremely important to establish the diagnosis. First, in the area of genetic counseling, Friedreich's Ataxia is usually transmitted by a recessive gene, thus affecting one of four children. This was borne out when he examined the six other siblings and found that a younger sister is also affected with the disease. Even though half of the offspring are hetereozygotes, they have a very small chance of producing affected individuals, since the gene frequency is low.

Prognosis

The importance of the diagnosis lies in the area of prognosis. Although the course does vary from individual to individual, the disease is usually relentless, and most patients become unable to walk by their late teens. Death usually occurs within twenty-five years of onset.

Treatment

It is important to make the diagnosis in order to be aware of and properly treat complications as they arise. These include foot deformities, scoliosis, and heart involvement. Cardiac disease occurs in 25-50 percent of patients as a nonspecific chronic myocardopathy. Death from cardiac failure is not unusual; however, this patient's electrocardiogram was

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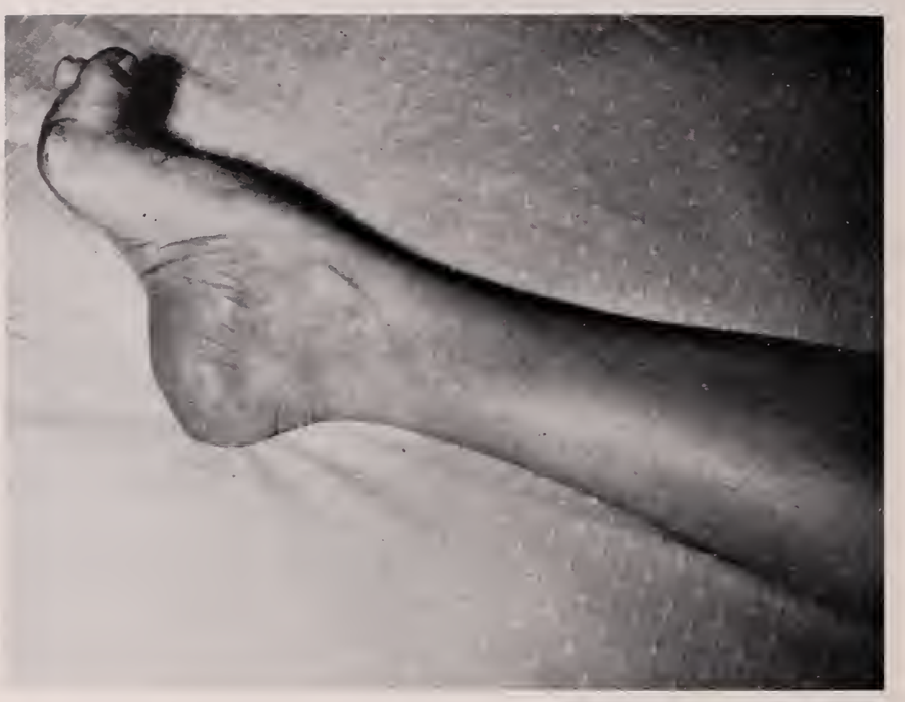

Fig. 2 — Pes cavus deformity in Friedreich's Ataxia

normal. Usually, if there is cardiac involvement, it is first evidenced in the electrocardiogram where reversal of T waves in leads V5 and V6.

Community Service Problem

Dr. Blaw pointed out the importance of this diagnosis and prognosis for the community to assess their resources for the handling of this child, who will probably be in a wheel chair as she emerges from adolescence. Certain orthopedic problems such as progressive foot deformities and scoliosis may appear, and further evaluation will be needed in these areas. Intellectual deficit, which may be progressive, will necessitate that school resources be flexible enough to meet this type of need. Dr. Blaw also commented on the value of hospitalization as a period of adjustment for the family. He pointed out that it was extremely important when such a diagnosis is made to give the family time to become adjusted to the implications.

Miss Josephine Kramer* discussed the educational resources available in Austin. There are special classes for retarded children in the Junior High and High schools, and home-care teaching is available if it is deemed necessary. At the present time, the patient is in regular classes and doing C and D work. She seems to perform her work quite quickly, although poorly. Miss Kramer asked what type of physical education program the child should be involved in. Dr. Blaw commented that certainly physical exercise and games were important, but that any activities which involve climbing or balancing should be avoided. He felt that programing should be flexible and gauged to the degree of neurological impairment.

Dr. Wentworth Quast** who performed the psychological testing of the patient, emphasized that there was no evidence of emotional problems, and for this reason, he did not feel that Minnesota Multiphasic Personality Inventory was necessary on the parents. He urged the school to consider keeping the child in regular classes for the next two years, having her participate in as many normal activities as possible. Further evaluation will be needed as her disease progresses.

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*Director of Elementary Education, Austin Public Schools.

**Child Psychologist.

Recommendations

1. Dr. Ray Van Cleve will maintain his role as the primary medical advisor for the family. Some type of periodic checkup for cardiac, orthopedic, and psychological evaluation will be made by him. If any further problems develop in this area, referral back to the University of Minnesota Hospitals will be considered. It is hoped that the community resources, however, will be able to provide the major medical care required. Dr. Van Cleve will also be the main source of counseling to the parents as regards any progression of the disease.
2. The school will adjust its educational program, taking into account the progression of the disease, a certain amount of normal physical exercise is encouraged; but a physical education program should be so flexible and restricted as to avoid any hazardous situations. As the disease progresses, homebound teaching or special transportation to school can be provided by the community.
3. As the disease progresses, a social worker or public health nurse may need to be consulted in anticipating and making arrangements for further care. At the present time, the school will function as a social worker until the child reaches Junior High School, when a regular social worker will be available on a full-time basis. A public health nurse may also be considered at this time.

Robert W. ten Bensel, M.D.
Department of Pediatrics
University of Minnesota Medical School

Participating in the Conference

Dr. Ray Van Cleve, Physician, Austin, Minnesota; Dr. Michael Blaw, Pediatric Neurologist; Dr. Daniel Murphy, Student Physician; Dr. Don Pearson, School Psychologist, Austin, Minnesota; Miss Josephine Kramer, Director of Elementary Education, Austin Public Schools; Miss Francis Baxter, Principal, Nevalyn School, Austin, Minnesota; Dr. Wentworth Quast, Child Psychologist; Dr. Robert ten Bensel, Moderator.

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The rung of a ladder was never meant to rest upon, but only to hold a man's foot long enough to enable him to put the other somewhat higher.—T. H. Huxley

We make way for the man who boldly pushes past us.—C. N. Bovee

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Advances

Bacteremia:
Microbes, Manifestations, and Methods of Management

Part III — Bacteremia Due to Some Less Commonly Encountered Organisms; Adjunctive Therapy

WILLIAM J. MARTIN, M.D.[**]
Rochester, Minnesota

Clostridia

Bacteremia due to organisms of the genus Clostridium has been reported in seven patients with underlying hematologic disease and in three patients with neoplastic disease.[15] However, the majority of reported cases of clostridial bacteremia have been associated with postabortal or puerperal sepsis.

General supportive care, including blood transfusions when indicated, and the administration of antibiotics and polyvalent gas-gangrene antitoxin have been recommended for management of clostridial bacteremia. Penicillin in massive doses appears to be the antibacterial agent of choice, but some investigators believe that a tetracycline may give additional benefit. Therapy with antimicrobial agents or antiserum is not regarded as a substitute for surgical extirpation of a septic focus. Placing the patient in a hyperbaric chamber in an attempt to increase the amount of oxygen in the tissues, particularly the oxygen in physical solution, has been advocated. Exposure to oxygen at three atmospheres of pressure for two-hour sessions is said to be safe and effective.

Bacillus Anthracis

Several antibacterial agents including penicillin, erythromycin, tetracycline, and sulfonamides have been effective in anthrax. Because penicillin is bactericidal and less toxic than a tetracycline or a sulfonamide, it may be the agent of choice if the patient has not previously had an allergic reaction to the drug.

Listeria Monocytogenes

Penicillin, tetracycline, and erythromycin each has been effective in infections due to this organism. Whether addition of streptomycin enhances the activity of penicillin or tetracycline is disputed.

Mimae (Mima polymorphia, Herrellea vaginocola)

In bacteremia due to these organisms a tetracycline alone may suffice, but in severe infections combined sulfonamidetetracycline or kanamycin-tetracycline therapy may be more efficacious when treatment is begun before in vitro susceptibilities are reported.

Vibrio Fetus

Infection due to this organism resembles brucellosis in its pathogenesis and symptomatology, and it appears best managed by a regimen similar to that used in brucellosis, namely streptomycin-tetracycline therapy.

Polymicrobic Bacteremia

Polymicrobic infections are most likely to occur in Bacteroides bacteremia and in infections of the blood due to Str. faecalis.

Treatment

In treatment of polymicrobic bacteremia, several drugs may be given simultaneously — for example, tetracycline in Bacteroides infection and, concomitantly, penicillin and streptomycin, against a streptococcus. Also, in addition to penicillin and streptomycin ad-

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[*] Parts I and II, Minnesota Med 47:9, page 1105 and 47:10, Page 1267.

[**] Section of Medicine, Mayo Clinic and Mayo Foundation.

ministered in a case of enterococcal bacteremia, one may add tetracycline against coli-aerogenes organisms. Since it is difficult to say which organism is most important in polymicrobic bacteremia, one gives broad coverage. However, one attempts to keep the number of agents minimal and resorts to such an antibiotic umbrella only rarely. The use of several agents not only is not necessary in all cases but also might increase bacterial resistance to a greater degree than would be the case if bacteremias were treated with a minimal number of antibacterial drugs. Indiscriminate use of multiple agents may increase bacterial resistance, since such resistance appears to be a direct function of the total amount of a given antibacterial drug used in a given community.

Perhaps ampicillin will have special application in future polymicrobic infections. In this same regard, cephalothin, the cephalosporin C derivative mentioned previously, shares with ampicillin the characteristic of being active against certain gram-negative bacteria as well as against strains of gram-positive cocci. Unlike ampicillin, cephalothin is active against penicillin G-resistant staphylococci. In addition, cephalothin has another theoretic advantage over ampicillin since cross-allergenicity exists among penicillins G and V, and the semisynthetic penicillins, including ampicillin. Cephalothin, which lacks the basic penicillin molecule of 6-aminopenicillanic acid, appears not to be cross-allergenic with these drugs and hence would be preferred over ampicillin in patients allergic to the penicillins.

Adjunctive Therapy of Bacteremia

Supportive Therapy

Pyrexia may be partially controlled by use of aspirin, cold spongings, and sedation. Tepid sponge baths may be helpful to patients with paroxysmal sweats. The febrile patient should remain in bed. The diet should be as liberal as the patient desires and his general status will allow, of high caloric value, and rich in protein and vitamin content. Therapy with iron may be indicated for posthemorrhagic anemia. Replacement of blood may be required. Fluid and electrolyte deficits may require correction; however, over-administration of fluids, especially saline solution, during a period of oliguria can cause death from embarrassment of cardiac function or from pulmonary edema. Psychotherapy is a supportive item not to be neglected.

Surgical Therapy

Surgical intervention may be of therapeutic aid when a primary or a metastatic site of infection must be drained. The gallbladder, the middle ear, or an obstructed portion of the urinary tract may become a nidus of infection from which the blood is reseeded with organisms, and nonsurgical treatment may prove inadequate. Metastatic suppuration requiring surgical attention is most likely to complicate bacteremia due to Staph. aureus, Str. pyogenes, or Bacteroides organisms.

Therapy for Shock

Although shock occurs in nonbacterial infections as well as in infections not characterized by bacteremia, it is emphasized herein as a complication of bacteremia. It is most likely to complicate staphylococcemia, meningococcemia, and bacteremia due to gram-negative bacilli. Of our three hundred and three patients with bacteremia due to gram-negative enteric bacilli, fifty-nine (approximately one in five) had bacteremic shock.[16] However, although the incidence of bacteremia due to these pathogens has increased in recent years, the incidence of bacteremic shock has increased to a greater extent. Currently, the incidence of the complication in this type of bacteremia undoubtedly is nearer one in three.

It is common knowledge that controversy exists regarding the precise management of bacteremic shock, but those measures frequently employed are mentioned, at least for the sake of completeness.

Support to the Circulation

Vasopressors have been used in an attempt to forestall so-called irreversible shock but also to restore circulation before ischemia has damaged the kidneys and produced renal shutdown. As will be noted later, a current question is whether vasodilators should be used rather than vasopressors. Older agents, such as epinephrine, ephedrine, and neosynephrine, are no longer in common use. Some newer agents such as mephentermine sulfate and methoxamine do not appear to be used as extensively as are metaraminol and levarterenol. Angiotensin appears to have potential in this regard. If one uses a Y-tube apparatus to deliver vasopressor drugs given intravenously, one can discontinue administration of the vasopressor periodically so that only a minimal amount is given, but the solution remains immediately available if hypotension recurs. Similar exactness of titration is not possible with subcutaneous or intramuscular administration of vasopressors. Empirically it seems wise not to attempt to raise the systolic blood pressure above 100 mm. of mercury in a previously normotensive patient.

Aramine

Metaraminol bitartrate (Aramine), unlike levarterenol bitartrate (Levophed), has been given intramuscularly and subcutaneously as well as intravenously. It is said to be less likely to result in dependence with reflex hypotension on withdrawal and is thought to promote renal blood flow more strongly. Despite these advantages, and the more important one of being less likely to cause tissue necrosis on extravasation, it has not completely displaced levarterenol in clinical practice. Levarterenol will maintain blood pressure in patients who are refractory to metaraminol or to mephentermine sulfate and in some cases to angiotensin.

Recommended initial doses for intramuscular or subcutaneous administration of metaraminol are 2 to 10 mg. (0.2 to 1 ml.). Doses for intravenous infusion vary from 15 to 100 mg. (1.5 to 10 ml.) given in 500 to 1000 ml. of fluid. Since the maximal effect of the drug is not apparent immediately, it is recommended that one wait at least 10 minutes before increasing the dosage. One should avoid injection of metaraminol into regions of arterial insufficiency, and it is advised that one not use the drug in conjunction with cyclopropane anesthesia because of the danger of precipitating ventricular fibrillation. Metaraminol should be administered cautiously to patients who have diseases of the heart or thyroid, previous hypertension, or diabetes. Some experimental findings suggest that release of levarterenol from sympathetic nerves plays a major role in the action of metaraminol. If this is correct, when refractoriness to metaraminol is suspected, one should substitute levarterenol. Since reserpine may deplete stores of levarterenol, metaraminol also may not be advisable in the management of patients who recently have received such catecholamine-depleting drugs.

Levarterenol

Levarterenol (arterenol, noradrenalin, norepinephrine) is given intravenously in increments of 4 ml. of a 0.2 per cent solution in 1000 ml. of parenteral fluid (usually 5 per cent dextrose in distilled water) at a rate sufficient to maintain the blood pressure at the desired level. Fluids containing dextrose protect against loss of potency by levarterenol due to oxidation; levarterenol should not be given in saline solution alone. More than a dozen ampules have been given per day to patients who remain hypotensive. An antecubital vein is the preferred site of infusion of solutions containing levarterenol; use of veins of the leg in elderly patients or in those with peripheral occlusive disease and of veins of the hand are to be avoided.

The site of infusion and the course of the vein infused should be inspected frequently for evidence of extravasation, such as a hard, cold, blanched area of skin. Infusion sites should be used in rotation if treatment is prolonged. If ischemia is noted, necrosis may be prevented or minimized if the infusion is promptly stopped and the region is infiltrated with adrenergic blocking agents. Injection of blanched areas with either 5 to 10 mg. of phentolamine (Regitine), with or without 150 turbidity units of hyaluronidase, or 5 mg.

Continued

of piperoxan (Benodaine) contained in 10 to 20 ml. of saline solution is recommended; injection is made with a long 22-gauge needle and is directed to all parts of the blanched area. Protection against necrosis of the skin following extravasation of levarterenol is said to be possible by adding 5 to 10 mg. of phentolamine, or 10 to 20 mg. of heparin, to each liter of solution containing the agent. Phentolamine used in this manner is said not to reduce the pressor effect of levarterenol despite antagonizing its local vasoconstrictor action. Levarterenol also should be used with caution in patients to whom cyclopropane anesthesia or other potentially cardiac-sensitizing agents recently have been administered.

Angiotensin

Angiotensin has given encouraging results in maintaining the patient's blood pressure during an episode of bacteremic shock. Some data from experimental animals have been interpreted as indicating that aldosterone may potentiate the vasopressor action of angiotensin. Angiotensin is thought to have stronger action on the visceral blood vessels in contradistinction to levarterenol, which chiefly affects blood vessels of the muscles. Unlike levarterenol, angiotensin is said not to induce dependence or reflex hypotension on its withdrawal. Although angiotensin has been given intramuscularly and subcutaneously without producing necrosis of tissue, usually it is given by slow intravenous drip. A vial of angiotensin contains 2.5 mg. of the drug, and one to four vials may be added to 500 to 1000 ml. of fluid. As many as ten vials have been given in a twenty-four-hour period. The rate of intravenous flow is regulated so that 1 to 10 micrograms are given per minute, with the usual amount being 3 to 5 micrograms; however, considerably larger amounts have been given in desperate situations. A response is evident in a few minutes in favorable cases, at which time one adjusts the rate of flow so as to maintain the desired blood pressure. Apparently, certain patients not responding well to levarterenol have responded to angiotensin, and, since the converse also has occurred in some patients, a trial of both drugs may be required.

Sympathetic Blocking Agents

Also, largely on an investigational basis, sympathetic (adrenergic) blocking agents, such as phenoxybenzamine (Dibenzyline), in amounts of 1 mg. per kilogram of body weight administered by slow intravenous drip, have been used in patients in bacteremic shock in the hope of inducing more normal redistribution of the blood flow which, in turn, will result in a restoration of the blood pressure to normal. Evaluation of these agents is being made because some findings, such as pallor, sweating, and tachycardia, are signs of vasoconstriction and overactivity of the sympathetic nervous system. Therefore, it has been theorized that dilation of blood vessels, rather than their further constriction by vasopressor agents, may be required to induce local redistribution of blood and speeding up of flow with relief of visceral pooling.

Other Supportive Measures

Oxygen

Oxygen therapy has been recommended to counteract tissue anoxia resulting from the reduced arterial blood flow, but the logic of its use is disputed.

Mechanical Measures

Elevating the foot of the patient's bed (shock position), application of an abdominal binder, and bandaging of the lower extremities are mechanical measures designed to increase venous return to the heart and, consequently, increase cardiac output. However, there are no exact data which indicate that these measures are of substantial benefit.

If hypothermia is not used, the patient may be kept comfortably warm, but overheating is to be avoided. Overheating may induce dilation of superficial vessels and further increase the capacity of the vascular bed. The exact application of hypothermia in bacteremic shock remains unclear.

In patients suffering from renal shutdown, usually the first sign of reversibility is re-appearance of excretory function within ten to twelve days. Excretory function reappears before regulatory function, and death with progressive azotemia and acidosis remains possible at this stage. Hemodialysis has contributed significantly to maintaining life and reducing morbidity during the oliguric phase of renal shutdown. It should not be reserved as a last desperate measure; its failure to prevent death may reflect belated use. Persistent oliguria may necessitate repeated hemodialysis.

Adrenal Steroids

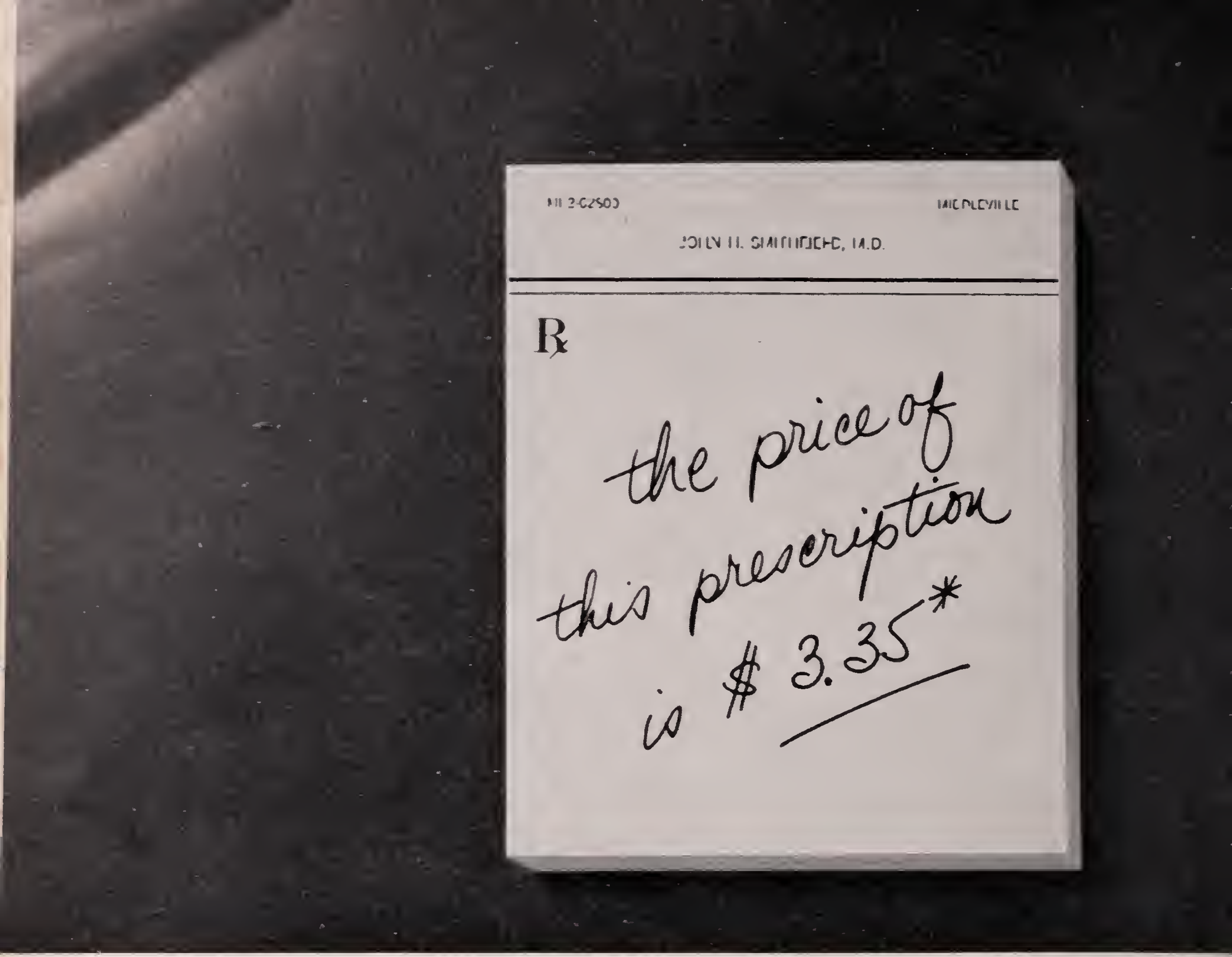
Some investigators note a favorable response to the use of adrenal cortical steroids in cases of bacteremic shock despite the fact that these patients, even when moribund, show no abnormality of the secretory function of the adrenal gland. We are not persuaded that use of these agents is mandatory on the fragile basis of comparing mortality rates in reported series wherein such steroids were employed. Actually, such comparison might lead one to conclude that patients who have received this type of steroid in attempts to control shock have a higher mortality rate. We have limited the administration of adrenal cortical steroids to those patients who had been receiving them before the occurrence of bacteremia and bacteremic shock. Also, we have not used blood, plasma, or dextran in the definitive management of this complication in our patients.

Conclusions

With the advent of effective antibacterial agents, the incidences of streptococcal and pneumococcal bacteremia have decreased considerably. This empty ecologic niche is being filled by a progressively increasing incidence of bacteremia due to gram-negative bacilli. In the management of patients having bacteremia, it is necessary that one be acquainted with the underlying or predisposing diseases and forms of treatment which may influence the type of infecting pathogen, hinder the patient's recovery from the infection, or require special therapeutic attention. The many facets of bacteremia, such as polymicrobic etiology, causation by organisms requiring anerobic culture technics, and the complication of bacteremic shock, also indicate the need for special knowledge on the part of the physician caring for patients with such infections. A primary nidus of infection, from which the bloodstream has been seeded, or a site of metastatic suppuration may require surgical intervention. "Cure" in a case of bacteremia is determined only by the patient's progress from both clinical and laboratory points of view after cessation of antibacterial therapy. Careful analysis of individual cases of bacteremia and the use of common sense in application of antibacterial drugs are required. At any stage in the management of bacteremia, it may be necessary to re-evaluate, re-examine, and alter any regimen.

I had six honest serving men —
They taught me all I knew:
Their names were Where and What and When — and
Why and How and Who. — Kipling

Though the mills of God grind slowly,
Yet they grind exceeding small;
Though with patience He stands waiting,
With exactness grinds He all. — Longfellow



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*Average prescription price, 1963. National Prescription Audit, R.A. Gosselin, Dedham, Mass.

Grand Rounds

Peritoneal Dialysis[*]

The first experimental work with peritoneal dialysis was done in 1877 by Wagner, followed by Starling and Tubby in 1894 and 1895. Their work showed that hypertonic solutions introduced into the abdominal cavity increased in volume and were found to contain both body proteins and salts. These changes did not seem to be guided solely by osmotic laws. A variety of perfusing fluids were used including such unphysiological solutions as 90% glycerine and 2% formaldehyde. No practical applications were attempted and the greatest interest lay in the discovery of both the method of formation and the composition of ascitic fluids.

In 1922 Putman published a report on the peritoneum as a dialysing membrane, with observations made on dogs and cats using various types of solutions, including saline and glucose of varying strengths.[19] He noted that in spite of relative neglect of sterile technique almost no infections occurred even when some animals were run as many as four times. Putman also found that the dividing line between fluids which increased or decreased volume was a saline solution of 1.5%, but discovered that in spite of the concentration of the fluid, it would be reabsorbed if it were left in the abdominal cavity for an appropriate period of time. Hypertonic saline solutions were found to be poorly tolerated, frequently resulting in severe electrolyte disturbances or pulmonary edema. Five to ten percent glucose proved to be well tolerated and removed large amounts of body water. Putman also noted that urea and potassium soon appeared in the perfusate and that 20% glucose, which proved to be quite irritating to the peritoneum, contained high percentages of albumin. Fluids introduced into the peritoneal cavity soon came into near equilibrium with the blood crystaloids; but all solutions, even if hypertonic, were absorbed before this equilibrium was complete. His work also showed that larger molecules did not appear to diffuse, with the exception of glucose and body proteins.

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[*] Medical Grand Rounds, Mt. Sinai Hospital, June 9, 1964.

Continued

He concluded that diffusion and resorption of materials into and out of the peritoneum was a combination of filtration, osmosis, cellular action, and lymphatic absorption.

In 1923 Gantner attempted the first human dialysis, using saline solutions with moderate success.[3] Because of ensuing complications such as fluid imbalance, pulmonary edema, infection, and electrolyte problems his method did not become popular. In spite of improved solutions, techniques, and antibiotics only 101 dialyses were reported from 1923 to 1948.[18]

In 1951 Grollman began his extensive work on nephrectomized dogs and improved both perfusing solutions and techniques until he was able to keep animals alive from 90 to 121 days by peritoneal dialysis. Modification of solutions has continued until at the present time three commercial fluids are available. The methods and mechanisms of dialysis as well as recent advances were discussed thoroughly by Maxwell in 1959 and by Boen in 1961, with little change to the present time.

Physiology

Peritoneal dialysis is primarily dependent on the osmotic transfer of diffusable materials through a semi-permeable membrane, although other factors such as phagocytosis, ultrafiltration and active absorption are involved. These are dependent also on the approximately 22,000 sq. cm. of area and such mechanical and electrical forces as perfusion pressures, membrane pore size and Donnan equilibrium. It has long been noted that fluids are absorbed completely from the abdominal cavity in about 20 hours in spite of their osmolarity.

Early investigators such as Wagner, Stanley, and others have shown that water could be removed from the body by the instillation of hypertonic solutions into the peritoneal cavity, and that prompt diffusion of solutes as well as water occurred both in and out of these solutions. So it became evident that the peritoneum was a diffusion site which could be used to remove or replace substances.

Early attempts were crude since there was poor understanding of the function of certain ions and of fluid balance in general.[5,14] At first it was assumed that continuous perfusion would be needed, although earlier investigators had shown that closed intermittent drainage was feasible. Solutions and techniques have improved until now peritoneal dialysis has come to be considered a safe and relatively simple precedure.

It was not until 1961, however, that the kinetics of transfer were carefully worked out by Boen. He stressed for the first time the importance of clearance and of flow rates, giving a rational explanation for the infusion times, and suggesting certain modifications of solutions and procedure for specific problems. From 32 human perfusion studies Boen did extensive work on the clearance rates of water, urea, potassium, creatinine, uric acid, phosphate, calcium, magnesium, and indican as well as studies of sulfates and proteins. He also investigated the absorption of bicarbonate and water as well as glucose, relating the rates of absorption and clearance to the volume of perfusate per unit of exposure time. These then were graphed and related clearance rates were calculated, using urea as 100. Figure 1 shows the comparative clearance rates and Figure 2 relates the urea clearance to the dialyzed volumes. These findings indicate that 3.5

liters per hour appeared to be the maximum volume for urea clearance, but that 2.5 liters per hour was more practical, both mechanically and economically.

Schumacher has more recently shown that in chronic dialysis 1.2-1.8 L/hr was adequate for the usual exchanges. Water on the other hand diffused very rapidly, and 10-20 minutes of exposure time was considered all that should be used — with an absolute maximum of 30 minutes. Glucose and bicarbonate also appeared to diffuse quite rapidly. An interesting phenomenon was noted concerning potassium, which initially dropped

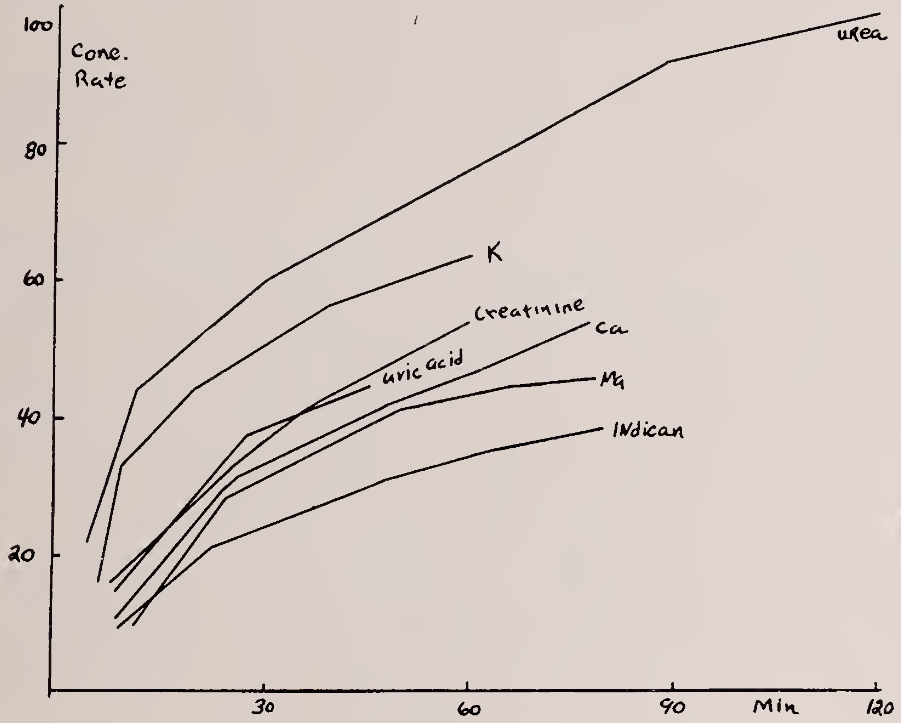

Figure 1

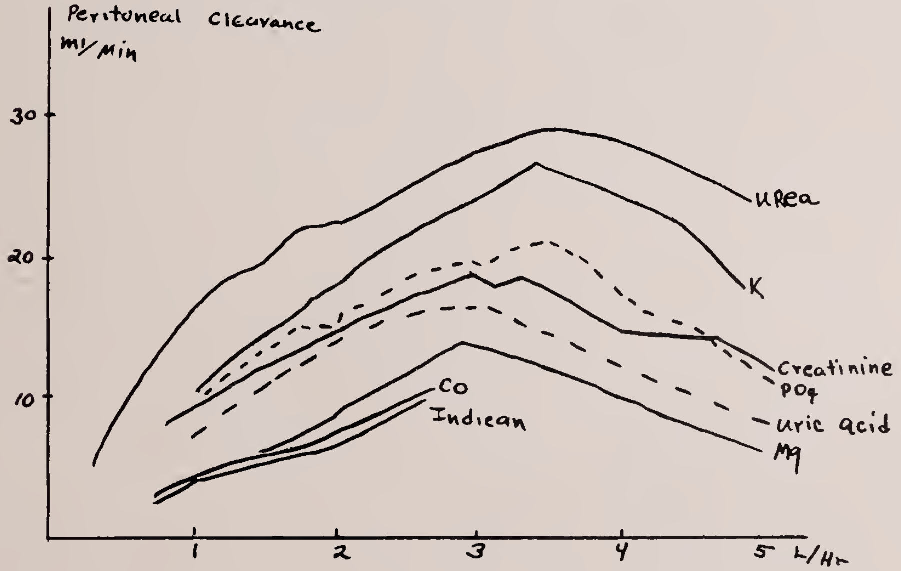

Figure 2

Continued

very markedly and then remained constant.[3] This was thought to be due to the slow elimination of potassium from cells and a possible explanation for the rapid return to elevated levels following hemodialysis. They[22] found that potassium-free fluids could be safely used for 24 hours without danger of depleting body stores, with resultant hypokalemia. Protein was found to diffuse into the peritoneal cavity at a rate of 0.5-1 grams per liter or 20-30 grams per 24 hours (1a,7).

Other investigators have found that the total protein loss per dialysis could run as high as 300 grams. Boen concluded that the difference between hemodialysis and peritoneal dialysis was quantitative and due to the following factors.[3]

1. Artificial kidney dialysis area was greater even though the peritoneal area appeared to be similar. This was because the vascular or effective dialysis area of the peritoneum was actually much below its total area.
2. Blood flow could be regulated in the kidney while the peritoneal flow was more or less constant.

He concluded that urea clearance is two to seven times greater in the "kidney," but that phosphate seemed to be cleared through the peritoneum at a proportionately greater rate than were other substances. The later finding was not marked, however, and he felt that the main difference between the two types of dialysis was in time required to remove equal amounts of metabolites. These differences and similarities are depicted in Table 1.

TABLE I

Comparison Between Peritoneal Dialysis and Extracorporeal Hemodialysis:Kinetics

	Peritoneal Dialysis				Wolf c.s. in vitro				Wolf c.s. in vivo			
	C (2.5/hr)	c	C.R. (30 min)	c.r.	D	d	E	e	D	d	E	e
Urea	26	100	0.61	100	300	100	0.60	100	204	100	0.69	100
K,	21	81	0.55	90	300	100	0.60	100	204	100	0.69	100
PO_4	16	62	0.38	62	92	31	0.18	30	77	38	0.26	37.7
SO_4			0.35	65	96	32	0.19	31.5				
Creatinine	15	58	0.37	61	169	56	0.34	57	123	60	0.42	60.8
	(14	55	0.38	62	135	45	0.27	45				
Uric acid	(26	100	0.57	93								
Ca	9.5	37	0.36	51	60-152	21-51	0.12 0.30	20-50				
Mg	11	42	0.33	47	100	33	0.20	33				
Phenol red					33	11	0.07	11.6				
Indican	8.5	33	0.25	40								
Glucose						40	0.24	40	82	40	0.28	40.5
Dialysing area M^2		1.73*					2.2				2.2	
Blood-flow ml/min						500				400		
Dialysed volume		2.5 L/Hr.					—				—	

*Peritoneal surface area

C = Peritoneal Clearance (at a dialysed volume of 2.5 L/Hr.)

$$c = \text{Clearance ratio } \frac{Cx}{C \text{ urea}} \text{ X } 100$$

$$\text{C.R. } \frac{\text{conc. peritoneal fluid}}{\text{conc. blood or plasma water}} \text{ (after a stay of 30 min. in abdomen)}$$

$$\text{c.r.} = \frac{\text{C.R. } x}{\text{C.R. urea}} \text{ X } 100$$

TABLE 2
Protein Loss into Peritoneal Dialysate and Changes in Plasma-Protein Concentration (Ia)

Pt. No.	Dialysis volume (litres)	Fluid protein conca. (g. per litre)	Total protein loss (g.)	Albumin loss (g.)	globulin loss (g.)	Plasma-total-protein (g. per 100 ml.) Before dialysis	After dialysis
1	14.8	0.68	10.1	6.8	1.0	6.0	5.5
2a	53.5	0.68	89.0	52.0	22.3	—	—
b	54.7	1.30	71.2	45.5	14.2	6.1	4.8
3	14.36	2.94	42.4	21.2	8.2	—	6.1
4	44.2	2.32	125.0	89.4	17.8	5.4	4.0
5	29.8	1.38	41.0	25.5	9.8	7.2	5.8
6	40.1	1.54	62.0	40.5	14.0	5.7	4.9
7	37.7	2.76	103.0	55.2	18.0	—	5.3
8	38.9	4.49	175.0	143.2	25.6	6.4	5.0
9	71.0	1.60	114.0	88.9	19.6	6.4	5.5
10	65.5	1.41	92.5	57.7	22.2	6.1	4.7
11	24.9	1.88	46.8	23.4	11.7	7.0	6.2
12	79.13	2.25	207.0	106.0	52.0	4.8	4.1

Recently it has been found that certain substances are removed more efficiently with alkaline media or by adding protein to the dialysate. The former is true of barbiturates with high PK values such as secobarbitol and the latter is true of protein-bound substances such as barbiturates and salicylates.[1,2,6,14] Barbiturates appear to diffuse more slowly than other substances and a longer period of exposure is recommended, one and one-half hours as opposed to the usual one-hour dialysis period.[1]

Technique

The technique of peritoneal dialysis is well described in Maxwell's paper and in the brochures of the Abbott, Baxter and Cutter Companies. These firms all produce a commercial peritoneal dialysis fluid under the respective names of Inpersol, Dianeal, and Peridiol. They are quite similar and have essentially the following composition:

	Meq/L	Osmolarity
Na	141.0	141.0
Cl	101.0	101.0
Ca	3.5	2.0
Mg	1.5	1.0
Lactate	45.0	45.0
Dextrose	15.0 (gm)	83.0
Total	292	372

It should be noted that the lactate gives approximately 40 meq. of bicarbonate per liter. The solutions are available as 1.5% and 10% dextrose, the latter being markedly hypertonic and rarely used. Since these solutions are made primarily for treating renal acidosis, potassium is absent and must be added as needed. All solutions utilize lactate in place of bicarbonate to maintain a pH of 5.1 to 6.1 so that calcium will remain in solution. In the adult 2,000 cc. of solution are utilized per exchange, after being previously warmed to body temperature.[16] Seven to ten minutes are usually required for instillation and the fluid is then left in the abdominal cavity for approximately 60 minutes, after which it is allowed to

Continued

syphon off, usually requiring another ten minutes. Immediately following the removal of the fluid two more previously warmed bottles of solution are put in place and the procedure repeated. Instillation of the fluid is accomplished through an abdominal catheter which is inserted into the abdominal cavity through the linea alba, approximately two inches below the umbilicus. Insertion of the catheter is through a #17 French trochar, after a small incision down to the fascia is made. A new thin-walled #14 trochar is now manufactured for this specific purpose. This trochar has the advantage of allowing the catheter to better fit the abdominal wound and decreasing leakage of solution.[9]

Larger wounds frequently require pursestring sutures to prevent leakage and occasionally one or two large mattress sutures to control immediate dermal hemorrhage. A curved catheter is then advanced into the region of the pouch of Douglas, making sure that all of the perforations are below the abdominal wall. If the midline is not available, stab wounds in the flank can be used, in which case it is considered advisable that the catheters be placed surgically. Surgical placement is also necessary if multiple adhesions are present. If the abdomen is flaccid and difficult to perforate, one or two liters of solution may be instilled into the abdominal cavity through a needle, prior to the placing of the abdominal catheter. Once the catheter is in place the tube is rinsed with heparinized saline or perfusing fluid to prevent plugging of the multiple small perforations. The heparin is continued during the first two exchanges and can then be discontinued unless the catheter needs to be replaced. The first two or three exchanges may be blood-tinged, but after that the fluid should be clear to opalescent. Observations of the volume and type of fluid should be carefully recorded as well as the time for instillation and complete drainage.

If at all possible the patient is weighed at least once daily to confirm observed changes in fluid balance. Careful monitoring of the blood pressure, pulse and respiration is recorded. A general rule is that increased pulse plus increased blood pressure with rales and gallop rhythm equals overhydration, while increased pulse with decreased blood pressure usually indicates underhydration.[19] Arrhythmias suggest electrolyte disturbance, usually potassium. In spite of the presence of severe acidosis, bicarbonate is seldom added, since the lactate seems to suffice. In some instances such as phenobarbital poisoning an elevated pH is of value in removal of ionized toxin. Pure bicarbonate added to the fluid is found to equalize so rapidly that the pH soon reaches neutrality, while the addition of the organic buffer THAM in a 0.074 molar concentration will maintain the perfusate above pH of 8.5.[2,14] This increases the clearance of the drug at least two-fold. Albumin has also been used for binding and removing certain drugs such as barbiturates and salicylates.[1,6] This is quite expensive, costing from $500.00 if Red Cross albumin is used to $3000.00 per dialysis period if commercial albumin is used.[2]

TABLE 3

Solu	THAM	pH5	NaOH pH10
Removal mg/10kg/hr.	29.1	15.9	19.5

Krochel (14)

Kennedy believes that convulsions during dialysis are frequently due to cerebral edema secondary to a disparity between removal of urea from the body fluids and from tissue cells, resulting in hypertonic cells which absorb great quantities of water, causing water intoxication.[15] This can be prevented by the addition of glucose to the perfusate, which both removes excess water and raises the blood sugar to 400 mg. per 100 cc., combating the difference in osmolarity. Urea could also be used but would make it difficult to assess the results of dialysis. If hypertonic fluids are used to remove water, intravenous albumin administration is suggested to prevent excessive vascular water loss and resultant shock.[16] Others also caution against indiscriminate addition of solutes to the perfusing fluids, since even one ampule of bicarbonate will raise osmolarity by 88 milliosmoles, with possible resultant dehydration.[16]

Indications

The indications for peritoneal dialysis have changed markedly as the procedure has become more routine and are continuing to change with wider acceptance as a form of therapy.

Acute renal shutdown with the rapid build-up of toxic materials is still best treated with the more efficient methods of hemodialysis, although even here dialysis may be used during the period required to move the patient to a center where hemodialysis is available, or tide him over while hemodialysis is being set up. It is also of use in severely ill patients unable to tolerate the physiologic stress of the artificial kidney. All indications and contraindications at the present time are relative; involved are time, cost, and availability of trained personnel as well as absolute medical and physiological reasons for considering dialysis. The relative safety of the procedure and the availability of commercial materials has resulted in a rapidly accumulating mass of information still not fully evaluated.

Boen has two separate groups of criteria for dialysis: acute renal failure and intoxication with diffusable substances.[3] Acute renal failure is divided into four groups: (1) potassium greater than 7 mEq/l, (2) gross overhydration, (3) severe acidosis with the bicarbonate less than 10 mEq/l, and (4) rapid deterioration. He reserves hemodialysis for acute and reversible lesions where rapid removal of metabolites is necessary. Blood urea values of 350-400 mg %, sulfate greater than 10 mEq/l, chlorides less than 85 mEq/l, and anuria longer than five or six days are absolute indications for dialysis. It has been stated that in spite of the availability of both types of dialysis, the recent survival rates following acute anuria are little changed because dialysis is not performed soon enough.[6,11] In chronic renal disease most investigators feel that acute exacerbations are an indication for peritoneal dialysis and that a rapid decline in condition is an indication for at least one dialysis, in the hope that correction of the metabolic disturbance may allow enough recovery of renal function to prolong life.[6,21]

Relative contraindications are recent surgery, peritonitis, and adhesions. Peritoneal dialysis has been done in all of these conditions and has been thought to improve an occasional case of peritonitis. Multiple adhesions usually require abdominal surgery for placement of catheters, and extreme loculation of the peritoneal compartment may make this type of dialysis

Continued

impossible. Hemorrhagic diasthesis is still considered more or less an absolute contraindication, although dialysis has been done in thrombocytopenia after platelet transfusions.[8] Abdominal hemorrhage, however, makes it impossible to continue dialysis, and if noted, dialysis should be stopped immediately.

The advantages of peritoneal dialysis are:[3,4,19]

1. Simple equipment which can be performed in almost any hospital setting with a minimum of skilled personnel.
2. Abrupt physiological changes of blood volume and electrolytes are avoided.
3. Composition of the dialyzing fluid can be easily and rapidly changed to fit the patient's changing condition. This avoids insufficient or over correction of water and electrolyte disturbances.
4. Dialysis can be prolonged when the patient has increased protein breakdown, removing newly formed waste products.
5. Repeated or prolonged dialysis may gradually bring intracellular products into balance which may not have time to equilibrate with more rapid hemodialysis.

The disadvantages of peritoneal dialysis are:[3,7,19]

1. Slower normalization rate may at times be a disadvantage.
2. The possibility of peritoneal infection is present although slight.
3. Possible intestinal perforation (rare).
4. Marked protein loss up to and over 40 grams per dialysis.
5. Fatigue from prolonged runs where the patient must remain in one position for long periods of time.
6. Absorption of large amounts of glucose during dialysis may drive potassium into the cells to be released at a later time. However, the glucose picked up from the dialyzing fluid will provide an energy source for the patient.
7. Cannot be used after severe abdominal wounds or extensive abdominal surgery.
8. Dialysis fluid must be sterile. This complication is not of great importance since commercial fluids are now available.

The artificial kidney also has its disadvantages since blood is required for its use and introduces the possibility of transfusion reactions. The high perfusion rates may result in hemorrhage, and since the artificial kidney acts as an arteriovenous fistula, it may overload an already damaged heart. Finally, there is a limited availability of blood vessels, and air embolism is an ever present danger.

Summary

Peritoneal dialysis has proven to be a useful therapeutic procedure in the treatment of renal failure and of intoxication with diffusable poisons. Its relative simplicity and economy have made it readily available to even small hospitals with modest equipment. It has been assuming a role of increasing importance as can be noted in a recent article from the Peter Bent Brigham Hospital where its use has greatly increased.[4] Such a simple procedure is almost certain to be over used and only careful evaluation of the situations which call for its use as well as a thorough knowledge of the physiology, pathology, complications, and moral implications will prevent its falling into disrepute and hamper further development.

TABLE 4

Year	H.D.	P.D.
1959	5	3
1960	102	21
1961	37	121

Burns, 1962 (4)
Peter Bent Brigham

Case Report

This 63-year-old white female was admitted to Mt. Sinai Hospital 4-18-64 because of weakness and oliguria for approximately one week prior to admission. The patient had been followed in the Outpatient Department and had had many prior hospitalizations for chronic pyelonephritis. She also was known to have hypothyroidism, for which she was taking 1½ grains of thyroid daily. She had also had myxedema since 1947, mild diabetes mellitus known since 1954, and had been treated intermittently for renal insufficiency secondary to chronic pyelonephritis since 1962. During October and November of 1963 she was admitted in renal failure and at that time developed severe rectal bleeding secondary to uremic ulcerations of the rectum.

Physical examination revealed a very drowsy, edematous white female who was moderately obese and pale. Fundi were negative without apparent arteriosclerotic or diabetic change. There was a moderate amount of periorbital edema. The neck veins were not distended. There were rales at both lung bases. The heart was not enlarged. The abdomen was soft, and the liver, kidneys and spleen were not palpable. There was mild edema of the ankles. Reflexes were hypoactive bilaterally but equal. Rectal and pelvic exams were within normal limits.

Laboratory Studies: hemoglobin 9.2 gm %, erythrocytes 2,900,000, leukocytes 18,900, 92% neutrophiles, 5 lymphocytes, 1 monocyte, 2 eosinophiles, sedimentation rate 119 mm per hour. Urine sp. gravity 1.012, pH 6, 2+ albumin, packed field white cells. Cholesterol 140 mg %. RBC indices revealed a normocytic, normochromic anemia. Urine culture revealed Klebsiella and Aerobactor. VDRL negative. Blood volume (Evans Blue) was 2,910 cc. White blood count on 4-23-64 had dropped to 11,700 with 83% neutrophiles. A repeat urine culture 4-27-64 revealed both organisms to be sensitive to Chloromycetin. Chest X ray revealed minimal left ventricular enlargement. Electrocardiogram showed left axis deviation and nonspecific T wave changes.

Date	Hg	HMt	BUN	Cr	Ca	PO$_4$	Na	K	Co$_2$	Cl$_2$	A/G
4-18	9.2	30.5	207								
4-20					7.3	10.3	139	4.6	4	102	
4-21 (Dialysis began)				17.5					2		
4-22	8.4	27.5	150				137	3.2	10	99	3/3.1
4-23	—		105	8.8	8.6		140	4.4		92	
4-24			78				142	3.5	23	96	
4-25 (Dialysis ended)			62				143	4.5	23	97	
4-27			89				143	4.6	20	98	
4-28			98							98	
5-7							143	3.9	16	104	
4-29	11.4										
5-15			129								

Hospital Course:

The patient became progressively more lethargic and on April 21 peritoneal dialysis was started. She was also being treated with Chloromycetin. After the first 24 hours of dialysis the BUN was down to 150 mg %. The CO2 combining power rose from 4 to 10. By the second day of dialysis the patient was responding and continued to improve until April 24, at which time the electrolytes were essentially normal with CO2 of 23 meq/L, potassium of 3.5 meq/L, and BUN 62 mg %, which was less than this patient's usual outpatient level.

The patient was dialyzed for a period of approximately 87 hours, receiving a total of 80 liters of dialyzing fluid, the first two liters of which were 7% dextrose and contained both heparin and achromycin. Following the third exchange, 4mEq of potassium were added to each liter of solution because of low serum potassium. During the first five exchanges, 1500 cc. of fluid were removed in addition to the dialyzing

Continued

fluid; following this the exchanges were positive or negative by ± 200 cc., except at the termination of the run, when there was a positive balance of as much as 800 cc. on two exchanges, thought to be due to leakage rather than to actual retention of fluid.

Following the initiation of dialysis the patient was alert enough to take fluids and be started on oral feeding and medication. The patient's BUN remained stable and no further dialysis was used. Although she had a low urine output of 400 to 700 cc. daily, she was discharged to her home, continuing on antibiotic therapy.

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11-23. Can be obtained from Grand Rounds Editor at Mt. Sinai Hospital.

Didacus of Seville

Though all saints on close acquaintance compel our admiration, occasionally one of them so transcends the dimensions of time and space as to make his personality as warmly and magnetically alive to us today as it must have been to those among whom he lived and labored in his own day. Such a one is Didacus of Seville, a Spanish Franciscan monk of the 16th century who was sent to the Canary Islands as a missionary. His term of faithful service there was interrupted by a pilgrimage to Siena, whither 4000 monks and friars flocked in a body to celebrate the canonization of St. Bernardine. Thereupon an epidemic disease broke out, and Didacus, instead of returning to the Canary Islands, remained at Siena to nurse the sick. Legend has it that he even cured the dying; also that inadequate supplies of medicine were miraculously increased through his power — reminiscent of Christ's multiplication of the loaves and fishes. Further, it was reported that in his ministrations Didacus kissed the contagious sores of his patients and when reproved by his superiors protested that kissing was the best way to cure.

Notwithstanding such rash physical contact, Didacus himself contracted no disease, but lived on to become infirmarian at Rome and to die a natural death there after long years of service.

His day is November 13.

Lots of people know a good thing the minute the other fellow sees it first.
—Job E. Hedges

Abstracts, Briefs and Commentaries

METHODS USED TO DIAGNOSE RENAL HYPERTENSION

One hundred and thirty patients with arterial hypertension were studied on the basis of (1) sudden onset of hypertension, (2) hypertension refractory to medical management, (3) hypertension occurring below the age of 40 years, (4) abnormal intravenous pyelograms, (5) history of trauma to the kidney, or (6) history of thromboembolic phenomena.

The authors used paracutaneous transfemoral retrograde renal angiography in 79 of the 130 patients. Four examinations were unsuccessful because of technical or occlusive arterial problems. The second method of investigation was differential ureteral catheterizations and renal clearance studies. The authors do not mention the exact number studied, but 16 patients seems to be the figure. The third investigation was by radioactive renograms. Fifty radioactive renograms were performed. There was one false negative and seven false positives among these 50.

The authors list the tests to differentiate the types of nephrogenic hypertension requiring both renal angiography and differential renal clearance test for proper medical and surgical treatment. Nephrogenic hypertension may result from:

1. Combined arterial and parenchymal disease affecting one kidney.
2. Bilateral arterial disease with unilateral renal ischemia.
3. Small kidney of undetermined origin.
4. Bilateral renal disease of different etiology in each kidney. (Right renal arterial artery aneurysm and left hypoplastic kidney.)

The authors outlined a diagnostic program for hypertension of renal origin. Preoperative individual ureteral catheterization was not considered necessary when renal angiography showed complete renal artery occlusion or when unequivocal unilateral renal artery stenosis was demonstrated. The routine use of differential renal function studies by individual ureteral catheterization was necessary following renal angiography in the following circumstances:

1. The abnormality demonstrated by renal angiography is minimum or equivocal.
2. Renal angiography demonstrates bilateral renal artery and/or kidney disease.

Continued

3. Two diseases involve a renal artery and/or a kidney unilaterally and
4. No abnormality is demonstrated by angiography, but there is strong clinical evidence of hypertension of renal origin or malignant hypertension is present which is refractory to medical therapy.

Renal differential studies were performed on 29 patients.

Twenty-six patients were operated upon without fatality. At present the safest and most reliable diagnostic program for evaluation of patients suspected of having hypertension of renal artery or kidney origin is renal angiography followed by differential renal clearance studies. The radioactive renal scanning did not serve as an adequate study for either a screening test or a reliable guide to evaluate the hemodynamic significance of a known lesion.

Jerome T. Grismer, M.D.
Minneapolis, Minn.

Stokes, J. M., Friedenberg, M. J., and Sunshine, H.: Comparison of Methods Used to Diagnose Renal Hypertension. AMA Arch Surg 87:238, 1963.

POSTURAL SYNCOPE

A study was made of postural syncope in a patient with a large postlaminectomy lumbar meningocele which communicated freely with the subarachnoid space. The transient loss of consciousness which developed almost invariably in the upright position was partially prevented by application of a tight fitting abdominal binder with an inflated pressure cuff directly over the meningocele. Sudden deflation of the pressure cuff with the patient in a semi-upright position immediately produced syncope with minimal changes in pulse rate, arterial blood pressure and electroencephalogram. These studies suggested that sudden pronounced reduction in cerebrospinal fluid pressure can cause sufficient mechanical disturbance of intracranial neuronal structures to produce loss of consciousness. Syncope in this individual was considered to be due to a "concussive" effect similar to that associated with head trauma and perhaps cough syncope.

Courtesy of References and Reviews
Journal of the American Medical Association

Klein, L., Woodhall, B., and Heyman A.: Neurology 13:146, 1963.

BREECH PRESENTATION

A review of 228 cases of breech delivery among primigravidas revealed a cesarean section rate of 7.45% (17) as compared to a section rate of 2.98% for the entire 27,641 term deliveries during the same 10-yr. period. There was no perinatal death or morbidity associated with cesarean section. The corrected perinatal mortality rate for 211 vaginal deliveries of breech presentations was 2.9% as compared with 0.33% for all vaginal deliveries at term in the 10-yr. period. There were no maternal deaths and only five cases of maternal morbidity. Factors which had some apparent relationship to perinatal damage were the increased risk to the fetus in cases of prolonged labor, especially with a large amount of sedation, and cases of breech extraction, particularly those performed because of prolapsed cord. It also is thought that X-ray pelvimetry was not utilized frequently enough.

Courtesy of References and Reviews
Journal of the American Medical Association

Verner, W. D.: Amer J Obstet Gynec 84:876, 1962.

ANATOMY OF THE LESSER SAPHENOUS VEIN

Although ten to fifteen per cent of adults over the age of 35 have varicose veins only a small proportion of these involve the lesser saphenous system. When incompetence of the lesser saphenous exists and requires surgery it is, of course, most important that extirpation be complete. Inasmuch as the proximal portion of this vein is sometimes difficult to delineate, and because considerable variation in its course has been noted, the authors elected to investigate the anatomy of the lesser saphenous vein.

They examined two hundred adult cadaver limbs, considering the course, fascial relations, and termination of the lesser saphenous vein in each.

Contrary to common opinion it was found that the vein had a wholly subcutaneous course in only 9% of extremities. In 91% it pierced the crural fascia below the knee. In 7% it pierced the crural fascia in the lower third, in 51.5% in the middle third, and in 32.5% in the upper third of the lower leg.

Multiple and variable communicating veins were found to connect the lesser saphenous to the greater saphenous and the deep systems.

Termination of the lesser saphenous was also found to be quite variable. It joined the popliteal vein in three fourths of the extremities studies. Twenty-seven per cent had muscular branches joining the terminal lesser saphenous in the popliteal fossa. Another 38% had communications with superficial or deep veins in the thigh, many of them equal in size or larger than the saphenous itself. One fourth of the lesser saphenous veins did not empty into the popliteal at all, but terminated in superficial or deep veins of the thigh or below the knee.

Variations in the relationship of the lesser saphenous vein termination to the tibial nerve were also common.

These anatomical observations have practical significance to the surgeon in the treatment of varicose veins. Disregard of these findings may lead to injury of the tibial nerve, deep vein trauma, incomplete lesser saphenous excision and recurrent varicosities.

The surgery of varicose veins is often lightly regarded and carelessly performed. The frustrating problems of improving an extremity with long standing chronic venous insufficiency impresses one with the importance of doing the best possible job the first time around. The studies outlined above merit serious study by the surgeon as they will enable him to more skillfully manage the effective stripping of the lesser saphenous system.

Robert N. Hammerstrom, M.D.
Minneapolis, Minnesota

Mossman, D. A., and Hartwell, S. W.: The Surgical Significance of the Subfascial Course of the Lesser Saphenous Vein. SGO 118:761, 1964.

SPHINCTEROTOMY FOR PANCREATITIS

The authors review briefly the history of sphincterotomy for recurrent pancreatitis, presenting nine years experience with use of sphincterotomy in the treatment of chronic recurrent pancreatitis in 23 patients, 16 of whom continued to have difficulty. They studied five patients on whom the operation was performed, using the technique described by Doubilet. None of these patients had associated biliary tract disease, cholecystitis, or cholelithiasis. Medical regimen had been attempted without success

Continued

even in those who abstained from alcohol. Three of the patients remained in follow-up and all had symptoms.

The authors then studied the physiological effect of sphincterotomy on biliary tract pressures in 26 patients. Their studies indicated that sphincterotomy did not result either in prolonged sphincteric inactivation or in diminished biliary tract pressure. Resting common-duct pressures were found to be essentially the same in patients having the sphincter of Oddi divided as in those either having it dilated instrumentally or having no manipulation at all. Likewise, the response of the sphincter of Oddi to constricting action of morphine and the relaxing action of Robinul were essentially the same in all patients studied, whether or not they had undergone sphincterotomy. Furthermore, the clinical course of patients undergoing sphincterotomy bore little correlation with the physiologic results the procedure had upon biliary tract pressures.

Therefore, the authors concluded that sphincterotomy had a limited role in surgical treatment of recurrent pancreatitis. Their policy was to perform a caudal pancreatogram and then select an operative procedure according to the X-ray finding. If the obstruction was located in the proximal portion of the pancreatic duct or in the papilla, sphincterotomy that included cutting the pancreatic ducts was performed. Any proximally located stricture was dilated. If the pancreatogram demonstrated multiple obstructions or strictures, distal to the first 3 cm. of the pancreatic duct and a dilated distal pancreatic duct was present, procedures that directly decompress the pancreatic duct into a defunctionalized segment of the bowel were utilized.

An example of critical clinical investigation.

Jerome T. Grismer, M.D.
Minneapolis, Minn.

Thistlethwaite, J. R., Smith, D. F.: Evaluation of Sphincterotomy for the Treatment of Chronic Recurrent Pancreatitis. Ann Surg 158:226, 1963.

TREATMENT OF CLUB FOOT

The uniform system of primary treatment applied to congenital club foot at the Orthopedic Service of the State University of Iowa consists in gentle manipulation and in the application of well molded, thinly padded plaster casts which are changed every four to seven days. The plaster is applied in two sections, one from the toes to just below the knees and the other covering the knee and thigh. The knee is immobilized at a right angle and the leg is gently rotated outward, to correct tibial torsion. The end-results achieved in 67 of the 322 patients treated during the 1948-1956 period are reported. These 67 patients, with a total of 94 severe congenital club feet, were followed up for periods of five to twelve years. In many instances a subcutaneous tendo-Achillis tenotomy was performed as part of the primary treatment. Tibial osteotomy was not necessary because medical tibial torsion was corrected by the application of toe-to-groin plaster casts followed by the use of Denis Browne splints. There was a first recurrence in 53 feet (56%), a second one in 17 (18%), a third in nine (10%), and a fourth in one foot. The recurrences were generally mild and responded to conservative treatment. No bone surgery was performed. The results were considered good in 71% of the cases; a slight residual deformity persisted in 28%, and in one foot the result was poor.

Courtesy of References and Reviews
Journal of the American Medical Association

Ponseti, I., and Smoley, E.
J Bone Joint Surg Amer 45 A:261, 1963.

ACQUIRED AORTIC STENOSIS IN ADULTS: FINDING OF PROGNOSTIC VALUE IN EVALUATION FOR SURGICAL TREATMENT

The authors analyze the data from 20 patients who underwent open heart aortic valve surgery. They analyzed a number of factors under the general headings of medical history, auscultation, electrocardiograms, X-ray films, and hemodynamics. A total of 17 specific findings under these categories were analyzed. Only six of the 17 findings showed the difference of 45% or greater between groups, and these were considered to have prognostic significance. These findings were, in order of decreasing difference between groups: (1) absent, or greatly diminished second heart sound in the aortic area; (2) left ventricular strain in the electrocardiogram; (3) peak systolic gradient across the aortic valve of 70 mm. of mercury or greater; (4) systolic upstroke duration in the brachial artery pressure tracing of 0.22 seconds or longer; (5) presence of calcification in the aortic valve on routine X-ray films; (6) poststenotic dilatation of the aorta on routine chest X-ray films. In seven of eight patients who died, four or five of these features were present, while such a combination occurred in only two of the twelve survivors. The authors concluded that these findings suggest that a delay of surgical treatment will increase the number of unfavorable features and so increase the operative risk, whereas operation with three or less of these present would reduce the risk to approximately 10%. The presence of four or five of the unfavorable features in a patient prior to surgery is associated with a surgical risk approximately seven times greater than risk in those in whom only three or less are found.

Comment: Further evaluation of this type is needed as guide lines for the surgeon. Once a person with an aortic valve lesion enters into congestive failure, even under the best of medical management, his life span is sharply limited to approximately two years. However, in this two-year period the patient becomes an increasing invalid or is often in danger of sudden death. It is also at this time that the patient becomes a rapidly poor risk insofar as open heart surgery is concerned. Even under the best of medical treatment this period is characterized by decrease in the cardiac output and increased deficiency of the myocardium.

The authors, unfortunately, did not comment as to the type of valvular surgery that was done other than that it was "open heart." They also did not associate the gradient as related to valve size or cardiac output at the time of catheterization. These studies would have been quite helpful.

Jerome T. Grismer, M.D.
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Calatayud, J. B., Schulz, K. J., Maranhao, V., Goldberg, H., and Mills, H.: J Thorac Cardiov Surg 47:337, 1964.

INTRAVENOUS CHOLANGIOGRAPHY AND ACUTE CHOLECYSTITIS-USE IN DIFFERENTIAL DIAGNOSIS

In 211 consecutive cases of acute abdominal pain, intravenous cholangiography as an emergency procedure was utilized. Two hundred patients were suitable for evaluation. Three types of radiologic findings were noted; there were: (1) opacification of the gallbladder and ducts, (2) opacification of the ducts only, (3) no opacification of the biliary tree. In those

Continued

studies in which the gallbladder and the ducts were visualized, acute cholecystitis was not present. Acute cholecystitis was indicated if there was visualization of the biliary ducts but no visualization of the gallbladder. No opacification of the biliary tree occurred in 40% of the patients examined; more than half of these patients had acute cholecystitis. Eighty-eight per cent of these individuals had disease in the right upper quadrant, either in the biliary tree or associated organs. The authors felt that intravenous cholangiography proved helpful and should be employed routinely in the management of patients suspected of having acute cholecystitis in whom emergency surgical procedures were contemplated.

Comment: Use of diagnostic tools is becoming increasingly important in cases of undiagnosed abdominal catastrophes in which there is doubt as to the exact etiology. However, one should not neglect the most important steps of clinical examination, careful history and observation, as these can never be replaced by laboratory tests.

Jerome T. Grismer, M.D.
Minneapolis, Minnesota

Harrington, O. B., Beall, A. C., Jr., Noon, G., and Debakey, M. E.: AMA Arch Surg 88:585, 1964.

AURICULAR NERVE REFLEX

To treat a cough intelligently the cause should be known. In children the cause is usually an upper respiratory infection, but, perhaps not rarely, it may be extrarespiratory.

A troublesome, gag-like cough in two boys, four and eight years old, could be reproduced by stimulation of the external auditory meatus. The cough was periodic, spasmodic and primarily nocturnal. Introduction of an ear speculum produced the cough at will. Such a stimulus affects Arnold's nerve, the auricular branch of the vagus nerve.

About one in 600 to 800 shows the reflex, but not all are troubled with a cough. It is thought that a foreign body, packed cerumen, eczema or other sources of irritation of the aural canal are necessary to produce the cough. It is suggested, however, that there may be other precipitating factors still unelucidated.

Courtesy of World Wide Abstracts

Smith, F. Michael: J Louisiana Med Soc 115/1:17-18

Administration of Medication by School Personnel

Minnesota State School Health Council has recommended a policy for the administration of medicine by the School Nurse:

1. Only when a child's health is jeopardized.
2. The nurse is to acquaint herself with the family and the identity of the disease.
3. Written statements from parents and from physicians are required.
4. No aspirin or other type medicines are to be prescribed.

It may be that the race is not always to the swift, nor the battle to the strong — but that's the way to bet. — Damon Runyon

Book Reviews

No book can be so good as to be profitable when negligently read. — Seneca

MEDICINE AND THE STATE —Mathew J. Lynch, M.D. and Stanley S. Raphael, M.B., 1963 by Charles C. Thomas.

The spectre of socialized medicine in the United States and arguments for and against it continue, often with little knowledge and objective data as to the problems involved. The two authors, both Canadian, but with English backgrounds, state very clearly in the preface that they are against government socialization of medicine and stand with the American opponents of socialized medicine. Although admittedly partisan, they present in their book a great deal of historical and factual material, both written and statistical, which will be of interest to both proponents and opponents of government socialized medicine. The authors have gone to great efforts to obtain reliable data to present a broad discussion and picture of the trends toward socialized medicine in the past throughout the western world and the problems created at the present time in those countries which have government socialized medicine. The development, results and effects of socialized medicine on the population and the physicians in Russia, England and the countries of Europe are discussed. The factors responsible for the institution of government socialized medicine in these countries are also described, as are the effects on medical education, the supply of medical students and of physicians. I found the book fascinating reading although presenting a rather depressing picture of the effects and results of socialization of the medical profession. Whether the proponents of socialized medicine can present an adequate rebuttal to the material in this book is a question to be answered. I would recommend this book very highly to all physicians, whether for or against socialized medicine, and also to the layman who obviously has a large stake in the future of medical practice in the United States. It is disturbing that apparently once governmental socialized medicine is instituted, a turning back toward free medical practice becomes very difficult, if not impossible.

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Minneapolis, Minn.

THE PATHOLOGY OF THE PULMONARY VASCULATURE — C. A. Wagenvoort, M.D., Donald Heath, M.D., Ph.D., and Jesse E. Edwards, M.D. Charles C. Thomas, Springfield, Illinois, $25.50.

This volume on pathology of the pulmonary vasculature is the only work of its kind in medical literature. Previously this topic has been included as a division of general or pulmonary pathology texts. Here for the first time the authors have brought together data, clinical information and photographs into a single volume, "The Pathology of the Pulmonary Vasculature."

The text is amplified by over 700 illustrations including photomicrographs, X rays and gross photos. Quality of reproductions in all instances is superb.

The contents are introduced by a complete resume of normal pulmonary vasculature at birth and the changes expected through childhood and into adulthood. Normal hemodynamics are also reviewed in this section. A complete chapter deals with methods of study of the pulmonary vasculature. The full spectrum of pathologic changes then follows. This includes pathology due to pulmonary hypertension, emboli, neoplasia, and changes due to primary pulmonary or cardiac diseases. Interwoven throughout this portion of the book is also a complete explanation of the concomitant hemodynamics.

This work certainly must rate as a pioneer in its field. Its comprehensive nature renders it an excellent reference text for all physicians dealing with the heart and lungs.

Theodore A. Peterson, M.D.
Minneapolis, Minnesota

COMMON COMPLAINTS — Smith, Kline & French Laboratories $3.00

As the title of this book implies, it is an excellent book for short reference and review of common complaints.

It is a "curbstone consultation" type of answer to a variety of items from snoring to low back pain.

Carl O. Rice, M.D.
Minneapolis, Minnesota

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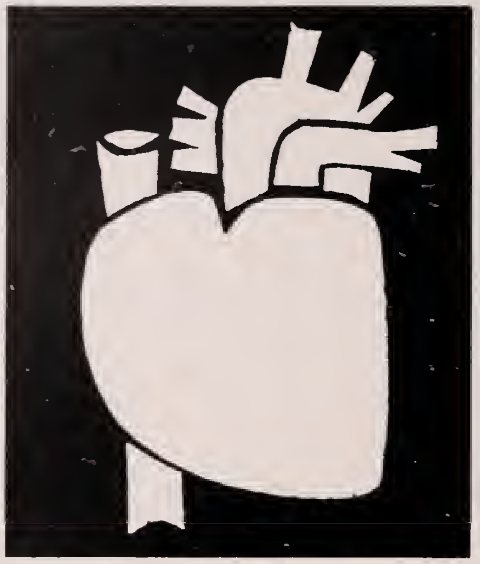

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IN ANGINA PECTORIS AND CORONARY INSUFFICIENCY

Provides long-term coronary vasodilation[1-11, 16]
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Indications: 'Miltrate' is useful for prophylaxis of pain in angina pectoris and coronary insufficiency, especially where anxiety is a factor. **Contraindications:** Like all nitrates, pentaerythritol tetranitrate should be avoided or prescribed cautiously for patients with glaucoma. Previous allergic or idiosyncratic reactions to meprobamate contraindicate subsequent use. **Precautions:** *Meprobamate* — Patients engaged in activities requiring alertness should be warned of drowsiness. Meprobamate may increase the effects of excessive alcohol, and the possibility of dependence should be considered, particularly in patients with a history of drug or alcohol addiction. Sudden withdrawal may result in reactions, rarely epileptiform seizures. Grand mal attacks may be precipitated in persons susceptible to both grand and petit mal. Prescribe cautiously and in small quantities to patients with suicidal tendencies. **Side effects:** *Pentaerythritol tetranitrate* — The most common side effects are transient headache, nausea, and rash. Weakness, palpitation, flushing, gastrointestinal distress, and lightheadedness have been reported on a few occasions. *Meprobamate* — May cause drowsiness and, rarely, ataxia, usually controlled by decreasing the dosage. Allergic or idiosyncratic reactions are rare, generally developing after one to four doses of the drug. Mild reactions include urticarial or maculopapular rash. Serious reactions, rarely encountered, include dermatological effects, acute nonthrombocytopenic purpura, chills, fever, fainting spells, angioneurotic edema, bronchial spasms, hypotensive crises, anuria, anaphylaxis, stomatitis and proctitis. Treatment should be symptomatic, and the drug not be reinstituted. **Dosage:** Usual dosage is one or two tablets before meals and at bedtime. Individualization of dosage is required for maximum therapeutic effect. Doses above twelve tablets daily are not recommended. **Supplied:** White tablets, each containing meprobamate 200 mg. and pentaerythritol tetranitrate 10 mg. *Before prescribing, consult package circular.*

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Perinatal Mortality Study

Coxsackie Virus Disease in the Newborn*

The mother of this infant was 26 years old, Rh positive, serologically negative for syphilis, and had had two previous normal pregnancies. During the present pregnancy the mother had had slight bleeding during the first and second trimesters, her hemoglobin ranged from 11.6 to 12.6 throughout pregnancy, and a urinalysis was negative for albumin. The infant was born occiput right anterior, low forceps assisted, after a normal labor. The first stage lasted three hours 30 minutes, the second stage five minutes. The membranes ruptured less than six hours before delivery.

The infant had an Apgar rating of 10 and his weight was seven lbs., one oz. The pediatrician found no abnormalities. The infant's hemoglobin was 18.6 gm.% on the day of birth, and he was put on formula feedings which he tolerated without difficulty. On the second day following birth, the nurses noted slight jaundice. On the third day, the mother ran a fever with temperature 101.80°, but examination and chest X ray were normal. Her fever continued with temperature 102°, the fourth and fifth days, at which time she was given Declostatin, 250 mgm., q.i.d. for eight doses. On the seventh day her temperature fell to normal and she went home on the eighth day.

The infant patient first developed a fever with temperature 100.6°, the sixth day after birth. On that day he had a chest X ray interpreted as normal; a throat culture which grew out nonhemolytic E. Coli and alpha streptocci; also a blood culture which was negative at 21 days. Further blood work revealed a hemoglobin of 20.9 gm.%, WBC 19,700 mm^3., with a differential of pmn-24, lymph-52, mono-10, eosin-1, baso-2. The blood bilirubin was one minute — 1.08, total 8.00 mg.%. Starting on the sixth day the infant was treated with procaine penicillin 200,000 units every 12 hours for four doses, and Chloromycetin 25 mg. every eight hours for seven. But he developed further jaundice, lethargy, poor sucking, and tachycardia, and expired on the eighth day after birth. He had no seizures at any time.

Autopsy Findings

An autopsy was performed within 30 minutes following death, with findings as follows:

Cardio Pulmonary

The heart weighs 25 gms. and it seems to be slightly enlarged. Its epicardial surfaces, particularly at the base of the heart, are liberally sprinkled with discrete and confluent petechiae. The ductus arteriosis is very small, but a lumen persists, and the foramen ovale is moderately patent. There is no anomalous state. The valves are normal and the endocardium and myocardium are normal except over the septum of the left

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*Hennepin County Perinatal Mortality Study Committee.

Continued

ventricle. Here there is a diffuse hemmorrhagic ecchymosis, and beneath the epicardium sectioning shows that the greater portion of the septal myocardium is also hemorrhagic.

The right lung weighs 42 grams. It remains fairly well aerated with irregular areas of atelectasis which are quite small and give the lung a mottled effect. The left lung weighs 30 grams. There are large areas of severe atelectasis.

Intraperitoneal

The spleen weighs 15 grams. Its contours are normal. On its surface there is a thin but definite fibrinous exudate. The cut surfaces are dark without any particular markings.

The liver weighs 125 grams and it shows no evidence of disease except a questionable very thin layer of fibrin on some of its surfaces. The cut surfaces show nothing abnormal. The gallbladder and ducts are normal.

Dissection of the sinus venosis and the omphalo-mesenteric vein reveals no evidence of any inflammatory or other disease. The umbilical cord stump is well dried and still slightly adherent.

The esophagus, the stomach, and the duodenum are normal. There is no noteworthy lymphadenopathy in the mesentery. The intestines are normal.

The pancreas and adrenals are normal. The adrenals together weigh five grams.

Each kidney weighs 15 grams. Fetal lobulation is quite marked, but there are no evidences of disease. The pelves, the ureters, and the bladder are normal.

There is no lymphadenopathy.

The thymus weighs 11 grams. It is free of petechiae and is grossly normal in every respect.

The trachea is normal and the larynx shows no evidence of edema or inflammation. There is no evidence of any obstruction.

The thyroid gland is normal.

Cranial

The scalp, the calvaria and the dura mater are normal. The anterior fontanel is small and slightly sunken. The posterior fontanel is closed. The leptomeninges are soft, transparent, and free from hemorrhage. The convolutions of the brain are normal. The hemispheres are symmetrical and of normal consistence. The structures of the base of the brain are normal. There is no evidence of swelling or edema. The folds of the dura mater in the base of the skull are free from tearing or hemorrhage. Sectioning of the fixed brain shows no abnormalities.

Cultures are taken of the heart blood, and smears are taken of the peritoneal fibrin and from the splenic substance. Lung tissue and intestine tissue are frozen for the Minnesota Department of Health virus studies.

Microscopic

In several brain sections there are conspicuous wide bands of lymphocytic infiltration about small venules or capillaries. Similarly scattered are small cellular foci of lymphocytes and glial proliferation. Some of these are in the vicinity of small arteries that appear thickened by increased adventitial and intimal cellularity.

The myocardial hemorrhage is confirmed. Even more conspicuous microscopically is a great increase in cellularity of the interstitial tissues, especially of the left ventricle with associated disruption and necrosis of myocardial fibers.

Some lung sections show mild edema with minimal exudate changes.

There are a few questionable proliferative foci in the liver portal space, spleen, pancreas, and kidneys.

Laboratory Data

The heart blood culture remains negative after 21 days of incubation.

The peritoneal smears show no bacteria or pus cells.

The Minnesota Department of Health Laboratories report the isolation of Coxsackie Virus, Type B-4, from lung tissue.

Diagnoses

Acute viral encephalitis due to Coxsackie virus, type B-4
Acute hemorrhagic interstitial myocarditis

Comment

Potter[1] states, "The first fatal Coxsackie infections reported were in South African infants observed during an epidemic in a nursing home at the same time that Bornholm disease was epidemic among adults. Since then both sporadic and epidemic cases in infants have been described, with a few cases resulting from transplacental infection.

"The symptoms in young infants are more severe than in adults, as is true of many viral infections, especially if contracted antenatally or during delivery. Among 25 cases collected from the literature by Kibrick and Benirschke of infants who became ill within three weeks of birth, six died within one day and only six recovered. Fever, feeding difficulty, and lethargy were the most common symptoms, with respiratory and cardiac disturbances occurring in about half and evidence of central nervous system irritation, hepatosplenomegaly and sudden collapse in one third. Meningitis was found in several infants who had no suggestive symptoms, indicating that it occurs more often than clinical observation would suggest. Among 15 infants on whom autopsy was performed focal myocarditis was found in all, focal meningoencephalitis in eight, hepatic necrosis or hepatitis in eight, pancreatitis in four and adrenal necrosis in one.

"Coxsackie virus, group B, type 4, was most commonly isolated, although a few cases were caused by types 2 and 3. Isolation was done by animal inoculation, and an unexpected finding in connection with inoculation with type 4 was that the animals developed severe destruction of anterior horn cells indistinguishable from poliomyelitis. The virus has also been recovered from several patients with symptoms of poliomyelitis, and the evidence seems to verify the original impression that the Coxsackie virus is capable of producing poliomyelitis-like lesions associated with muscle weakness in man.

"The lesions in the liver are usually striking and vary from mild irregular areas of necrosis, most often located near the central veins, to a devastating necrosis in which only a few cells immediately adjacent to portal areas are unaffected. The necrotic areas are less well circumscribed

Continued

than those of herpes virus infections. The adrenal glands are generally not involved and inclusions are usually absent.

"Myocarditis is rare in young infants, and since it has been found in nearly every case of proved Coxsackie infection one might be justified in considering every case of myocarditis in the newborn to be due to this cause until proved otherwise."

Schaffer[2] states concerning Coxsackie disease in the newborn, "Fever, anorexia and vomiting initiate the illness. Often signs of heart failure, with rapidly enlarging heart and liver, diminishing strength of heart sounds and electrocardiographic changes of myocardial damage follow. In some infants the most prominent signs are the vomiting, lethargy and convulsions of meningoencephalitis. Pneumonitis is marked by dyspnea, cyanosis, rales and patchy infiltrations by X-ray film. Hepatomegaly, mild to moderate jaundice, elevated bilirubin in the blood, a fair proportion of which is conjugated, and a lengthened prothrombin time with evidences of bleeding into skin and elsewhere indicate widespread involvement of the liver by the same inflammatory process.

"In some, the Coxsackie virus manifests a stronger affiliation for the myocardium than to any of the other infective agents which strike the newborn. The virus also produces meningoencephalitis, pneumonitis, and hepatitis. Rapid heart failure from myocarditis in the course of a generalized infection suggests the diagnosis of congenital Coxsackie virus disease very strongly. If the mother or some other member of the family had within a week of the infant's illness suffered from an influenza-like infection, the suspicion is strengthened, especially if pleuradynia had been part of the adult's symptomatology.

Summary

1. Coxsackie virus disease should be suspected in all newborns and young infants who develop myocarditis or meningoencephalitis, particularly if the mother had unexplained fever within one week of delivery.
2. Stool specimens should be sent to the Minnesota Department of Health Laboratories for virus isolation and identification in suspected cases of Coxsackie virus disease. Special containers supplied by the Department of Health should be used.
3. If the infant dies, organ sections should be frozen and sent for virus isolation and identification before any formalin or embalming fluid is used on the body. Additional information concerning collection of specimens may be obtained from the Minnesota Department of Health Laboratories.
4. There is no specific treatment for Coxsackie virus disease at this time.

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1. Potter, Edith L.: Pathology of the Fetus and Infant, Second Edition, 1961, Year Book Medical Publishers, Inc., p. 124.
2. Schaffer, Alexander J.: Diseases of the Newborn, 1960, W. B. Saunders Company, p. 661.
3. Cramblett, Henry G., et al.: Coxsackie Virus Infections. J Pediat 64:406, 1964.

The patient who consults a great many physicians is likely to have a very confused state of mind. — Rhazes (865-925)

Special Article

Observations on the Serum Cholesterol Levels in East African Natives

HERBERT W. JOHNSON, M.D.
St. Paul, Minnesota

INASMUCH as there is continuing controversy concerning the effect of the fat content of the diet on the serum cholesterol, and since there is either intense conviction on the part of some physicians or lack of conviction on the part of others that dietary fats, serum cholesterol, and arteriosclerosis are intimately related, it was felt that there was merit in reporting a series of cholesterol determinations on an African tribe heretofore not studied.

The author, while on a recent volunteer medical trip to the Lutheran Mission Field in Tanganyika, East Africa, had the opportunity to draw blood samples for cholesterol determinations on three groups of male natives. All groups were from the same region and same tribal background but separate and distinct in so far as occupation and diet were concerned.

The Characteristics of the Examined Group

The men of the Iramba tribe are typical of the central Tanganyikan area. On inspection their nutrition is good; they average five feet six inches to five feet eight inches in height. They tend to be slender and are beset with the usual bacillary and amoebic dysenteries of the area, malaria, and numerous parasitic infections. There are in general no emotional pressure problems in their tribal living, and the women of the tribe do most of the physical work.

Hospitalized Patients Group I

The first group of natives tested were all hospital patients. Their illnesses varied but were largely chronic infections of the types previously mentioned. This group of individuals were so-called "bush natives": that is, they lived in a tribal village away from civilization as we know it. Their diet consists largely of corn or millet mush made with water, vegetable soup, sweet potatoes, and a small amount of peanut oil. For all practical purposes no milk or dairy products are consumed, and almost no meat is eaten, since wild game is not easily obtained in the area.

Continued

The same diet was continued during their hospitalization, since the hospital has no dietary service; the patients' families follow them to the hospital and cook for them while they are there. The average age of the patients in this group was forty-four years.

The Male Nurses Group II

The second group tested were men of the same tribe who had decided to leave their bush existence and go into nurses' training at the same hospital in which the first group were patients. Nursing is largely a masculine profession in this area. Relatively the same diet was fed by the nursing school kitchen to this second group as to the first group. This may seem somewhat strange; but it should be remembered that the native is raised on this food; he enjoys it; he tolerates it well; it is high in protein; and from an economic standpoint it is a great deal more feasible to utilize the food at hand than to import animal protein with its initial high cost plus refrigeration problems on a small station that has electricity only two to three hours a day. The important difference between the two groups was the daily pressures to which the men in the second group were subjected. They were forced to adhere to a time schedule; they were responsible for having things done on time; they attended classes and took tests as our students do. This was an alien existence to them; having been brought up in the bush, they were now striving to advance their station in life. The average age in this group was twenty-five years.

The Affluent, Group III

The third group were men of the same tribe who occupied positions of greater responsibility in the hospital. They had had higher education corresponding to our high school level with one or two years of additional training in medicine or laboratory procedures. They experienced pressures in living similar to or only slightly greater than the men of the second group and enjoyed a relatively high pay scale and thus a higher standard of living. Their diet was markedly different than that of either of the first two groups.

TABLE I

Serum Cholesterol Levels in Natives on Varied Diets and Stress Situations

	Group I			Group II			Group III		
	Serum Cholesterol Mgm%	B.P.	Age	Serum Cholesterol Mgm%	B.P.	Age	Serum Cholesterol Mgm%	B.P.	Age
1.	108	90/70	40	127	120/70	22	117	118/90	21
2.	138	110/72	35	92	110/70	19	124	122/98	25
3.	124	96/74	26	147	140/90	20	200	142/98	35
4.	123	116/72	32	129	120/80	23	366	118/86	24
5.	161	130/82	50	140	120/80	22	197	118/80	28
6.	124	120/74	50	142	118/80	20	234	116/78	38
7.	116	110/68	42	123	130/70	19	103	120/90	38
8.	67	100/52	50	107	134/70	20	215	136/104	26
9.	187	120/92	30	98	108/80	23	153	126/90	34
10.	80	110/68	70	134	130/80	30	138	116/72	20
11.	120	70/52	48	110	110/70	27			
12.	276	150/96	70	102	120/90	29			
13.	130	100/60	29	107	108/70	20			
14.				99	120/80	20			
15.				198	124/80	20			
16.				138	110/60	19			
17.				137	112/78	28			
18.				99	118/80	34			
19.				124	120/82	60			
Av.	134	109/72	44	123	119/77	25	184	123/88	29

They ate meat daily and at least one egg a day. They drank fresh whole milk daily for at least six months a year and used powdered milk for the other six months. Two or more cups of peanut oil were used daily and occasionally butter. The average age of this group was twenty-nine years.

There were no cardiac complaints among any of the individuals tested. Physical examination of the heart and peripheral vessels was normal. An electrocardiogram was not done since no machine was available.

The Results

Table 1 shows the serum cholesterol values, the age of the individuals, and the average blood pressure reading in each instance.

It is immediately apparent that the average serum cholesterol is significantly higher in the third group, and that it is in this group that elevations in the diastolic blood pressure are noted, although not necessarily related to the cholesterol level.

Low in Saturated Fats

It is interesting to note that in Groups I and II who exist on a diet low in saturated fats, the average serum cholesterol levels were very similar and quite low by our standards of normality in spite of the fact that the second group were under considerably greater stress in their life situation. On comparing Groups II and III wherein the stress situation so far as occupation is concerned was similar but in which the diet was different, it is to be noted that the group which added saturated fats to their diet (Group III) showed a distinct elevation in serum cholesterol; and several of them showed elevations in diastolic blood pressure.

Conclusion

It would appear in this series, at least, that the elevation in serum cholesterol was related to the inclusion of saturated fats in the diet and that the addition of stress factors to the life situation did not appear to influence the cholesterol level. It is to be noted that elevations in the diastolic blood pressure occurred in the group with the highest serum cholesterol and in the two natives with definitely elevated serum cholesterol in Group I.

I am indebted to Dr. Henry L. Taylor of the Laboratory of Physiological Hygiene of the University of Minnesota for his kindness in running the serum cholesterol studies for me.

SEMINAR ON ALCOHOLISM

Fairview Hospital

November 28, 1964

9:30 A.M.

Speakers: R. C. Bell, M.D., Toronto
Donald Hastings, M.D., University of Minnesota
Donald Peterson, M.D., Willmar State Hospital

All doctors are urged to attend

If I shoot at the sun I may hit a star.—P. T. Barnum

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QUINETHAZONE·TABLETS
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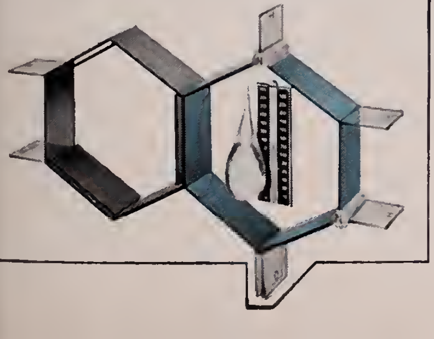

HYDROMOX Quinethazone is excellent for use in early hypertension. Extremely well tolerated, the average reported reduction in diastolic pressure is 15 mm. Hg,[1,2] just right for patients with mild to moderate diastolic elevations. Systolic pressure lowered accordingly. A convenient, single daily dose of one to two 50 mg. tablets is usually sufficient.

INDICATED in hypertension with or without edema, and in all types of edema involving salt retention. May be helpful in some cases of lymphedema, idiopathic edema and edema due to venous obstruction.

SIDE EFFECTS: Skin rash (rare), gastrointestinal disturbances, weakness and dizziness, seldom so severe that drug should be stopped. Generally, the adverse effects sometimes associated with the thiazide diuretics are possible. Pre-existing electrolyte abnormalities may be aggravated.

CONTRAINDICATION: Anuria.

1. Steigmann, F., and Griffin, R.: Evaluation of Quinethazone, a New Diuretic. J. Amer. Geriat. Soc. 11:945 (Oct.) 1963.

2. Schwartz, M.: Office Evaluation of a New Diuretic in Patients with Hypertensive Diseases. Scientific Exhibit Presented at the Clinical Meeting of the American Medical Association, Los Angeles, California, Nov. 25-28, 1962.

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Of 507 patients with confirmed ear, nose and throat infections... 465 or 91.7% were treated successfully with Signemycin®

Note:
Adams,* whose 50 patients included 20 with ENT infections, stated that Signemycin "was particularly valuable in infections that did not respond to other antimicrobial agents, and in patients to whom penicillin could not be given." All his cases responded within five days; in most patients, all signs of infection disappeared in three days.

*Adams, J.: J. Tenn. Med. Ass. 50:446, Nov., 1957.

Condition	No. of Patients	No. Cured with Signemycin
Otitis media	90	86
Pharyngitis and laryngitis	162	148
Sinusitis	68	55
Tonsillitis and peritonsillitis	163	153
Various	24	23
Totals	507	465 (91.7%)

consistently effective...often when others fail

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tetracycline HCl, 167 mg.; oleandomycin as triacetyloleandomycin, 83 mg.

capsules (250 mg.)

Also available as Syrup, Pediatric Drops, and half-strength Capsules

Brief Summary and Bibliography follow.

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Meetings and Announcements

No man can be provident of his time, who is not prudent in the choice of his company.—Jeremy Taylor

NOVEMBER

University of Illinois College of Medicine at the medical center will conduct a postgraduate course in laryngology and bronchoesophagology, November 9-21. Write the University; 1853 West Polk Street, Chicago 60612.

AMA Sixth National Conference on the medical aspects of sports, Deauville Hotel, November 29, in Miami Beach, Florida. Write: AMA, Chicago.

American College of Chest Physicians (interim meeting), Fontainebleau Hotel, Miami Beach, Florida, November 28-29. Exec. Dir.: Murray Kornfeld, 112 E. Chestnut, Chicago 11.

American Psychiatric Association, Bellevue Stratford Hotel, Philadelphia, November 20-21. Info.: Philip Mechanick, M.D., Ford Rd. and Monument Ave., Philadelphia.

Radiological Society of North America, Palmer House, Chicago, November 29-December 4. Sec.-Treas.: Maurice D. Frazer, M.D., 1744 S. 58th St., Lincoln, Neb.

Minnesota Department of Health, Management of Newborn & Premature — Seminar for Nurses — Dr. H. H. Reed, 1:30-4:30 p.m., St. Mary's Hospital Duluth, November 17.

Minnesota Academy of General Practice, Southeastern Chapter — 4:00 p.m., Rochester, November 17.

Minnesota Academy of General Practice, CCOC — Component Chapter Officers' Conference — 4:00 p.m., Leamington Hotel, Minneapolis, November 21.

Minnesota Academy of General Practice, Southern Chapter — 4:00 p.m., Mankato, November 24.

Minnesota Obstetrical and Gynecological Society, 9:00 a.m. — Capp Towers Motel, Minneapolis, November 28.

Ramsey County Medical Society, Election of Officers-program — 8:00 p.m. 15th Floor Lowry Medical Arts Building, St. Paul, November 30.

DECEMBER

Minnesota Academy of Medicine, Regular Meeting — 7:00 p.m., Town & Country Club, St. Paul, December 9.

St. Louis County Medical Society, Executive Comm. — 6:00 p.m., St. Luke's Hospital, Duluth, December 10.

Minnesota Society for Crippled Children and Adults, Inc., (Planning Rehab. Services for Mentally Ill and Mentally Retarded) 9:00 a.m. to 4:30 p.m., Ambassador Hotel, Minneapolis, December 16.

St. Louis County Medical Society, Dinner Dance — 7:00 p.m., Kitchi-Gammi Club, Duluth, December 19.

Ramsey County Medical Society, 8:00 p.m., 15th Floor Lowry Medical Arts Building, St. Paul, December 28.

Academy of Psychoanalysis, New York, December. Sec.: Alfred H. Rifkin, M.D., Academy of Psychoanalysis, 125 E 65th St., New York 21.

American Academy for Cerebral Palsy, Americana Hotel, New York, December 9-12. Sec.: J. D. Russ, M.D., 1520 Louisiana Ave., New Orleans 15.

American Academy of Dermatology, Palmer House, Chicago, December 5-10. Sec.-Treas.: Stanley E. Huss, M.D., 636 Church St., Evanston, Ill.

ANNOUNCEMENTS

Applications being received for Wyeth Pediatric Residency Fellowships that will begin on July 1, 1965. Each fellowship provides $4800 over two years toward advanced study required for board certification. Information: Dr. Philip Barba, University of Pennsylvania School of Medicine; Philadelphia, Pa. 19104.

* * *

American Society of Oral Surgeons announces presentation of cash awards for manuscripts concerning any phase of research related to oral surgery completed during the current year. Write: American Society of Oral Surgeons, 919 North Michigan, Chicago.

Of 1,088 patients with confirmed skin and soft-tissue infections... 1,036 or 95.2% were treated successfully with Signemycin®

Note:
Morador et al.* obtained *excellent results in the treatment of 185 out of 191 soft-tissue infections,* all due to staphylococci. They state: "In the most serious infections occurring in patients with impaired resistance (mainly diabetics) we have had very good results in the control of the infectious condition." In these studies, incision and drainage were employed where indicated.

*Morador, J. L. et al.: Antibiot. Ann. 1959-1960:716.

Condition	No. of Patients	No. Cured with Signemycin
Abscesses, various	35	34
Abscess, gluteal or perianal	54	52
Burns, infected	331	307
Carbuncles and furuncles	125	122
Cellulitis	104	102
Lacerations and wounds, infected	142	128
Ulcers, infected	107	106
Various superficial infections	190	185
Totals	1,088	1,036 (95.2%)

consistently effective...often when others fail

Signemycin®

tetracycline HCl, 167 mg.; oleandomycin as triacetyloleandomycin, 83 mg.

capsules (250 mg.)

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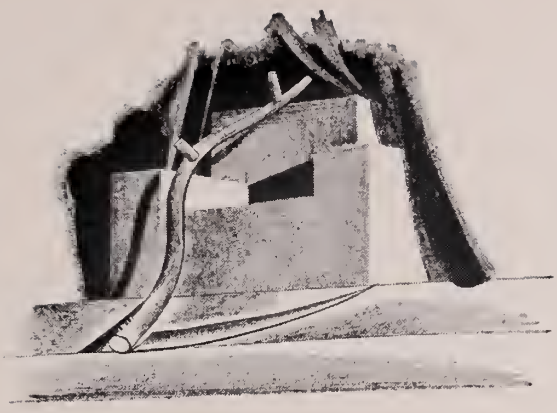

In Memoriam

Death is not to the Christian what it has often been called "Paying the debt of nature." No, it is not paying a debt; it is rather like bringing a note to a bank to obtain solid gold in exchange for it. You bring a cumbrous body which is worth nothing and which you would not wish to retain long; you lay it down, and receive for it, from the eternal treasures, liberty, victory, knowledge, and rapture.
— John Foster

WALTER E. HATCH

Dr. Walter E. Hatch, 81, prominent Duluth physician and surgeon for more than forty years, died September 16th. He had practiced medicine in Duluth since 1918 and had been urologist at St. Mary's, St. Luke's and Miller Memorial hospitals in Duluth. He was born at Baraboo, Wisconsin, and graduated from Northwestern University school of medicine.

Dr. Hatch was a past president of the St. Louis County Medical Society, a past president of the Twin City Urological Society, a director of the Duluth Venereal Disease Clinic and urological consultant at Middle River Sanitorium, Middle River, Wisconsin. He was certified by the American Board of Urology and elected a fellow of the Academy International of Medicine. He was a member of the Ionic Lodge AF&AM, the American Medical Association, North Central Branch of the American Urological Society, a past president of the Inter-Urban Academy of Medicine and a Life and 50 Club member of the Minnesota State Medical Association.

He is survived by his wife, a son and a daughter.

WALE S. WRIGHT

Dr. Wale S. Wright, 55, Minneapolis general practitioner, died September 16th. He was born in Minneapolis and graduated from the University of Minnesota Medical School.

He practiced in Minneapolis for thirty years and served on the staff of Swedish hospital. Dr. Wright retired a year ago because of illness. He was a member of the Hennepin County Medical Society, Minnesota State Medical Association and American Medical Association.

He is survived by his wife, a daughter, and his father, Dr. S. A. Wright of Minneapolis.

CHARLES W. FOGARTY

Dr. Charles W. Fogarty, 86, St. Paul ENT specialist, died September 17th. Born in Minneapolis, he was a resident and practiced medicine in St. Paul for more than fifty years. He was former chief of staff at St. Joseph's hospital and with the late Dr. William C. Carroll, he founded the St. Paul Clinic.

He was a member of the Ramsey County Medical Society, American Medical Association, American Academy of Ophthalmology and Otolaryngology and a fellow of the American College of Surgeons. He was a life and 50 Club member of the Minnesota State Medical Association.

He is survived by his two daughters and two sons, one of whom is Dr. Charles W. Fogarty, Jr. of St. Paul.

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Condition	No. of Patients	No. Cured with Signemycin
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Skin and soft-tissue infections	1,088	1,036
Bone and joint infections	71	64
Deep-seated or generalized infections	257	251
Obstetrical & gynecological infections	341	320
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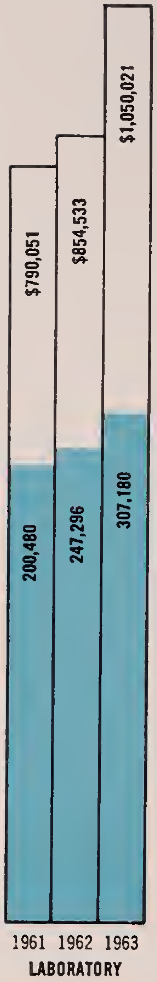

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History of Medicine

William Osler

1849-1919

Part II*

In 1905 Osler received the Crown appointment to become Regius Professor of Medicine at Oxford. Overworked for some time, he hoped to have a more relaxed life in England. "Life in Oxford was soon to be almost as full as before, and, as consulting practice again began to grow, was not as restful as Osler had expected. A quiet enjoyment, however, pervaded all his activities — the almshouses at Ewelme, of which he was Master, the proximity of the Bodleian, the collegiate life in Christ's Church, together provided an academic background which gave him intense satisfaction. His house in Norham Gardens soon became known as 'The Open Arms' . . . indication of the hospitality enjoyed by his innumerable friends. A baronetcy was conferred on Osler in 1911. . . ."[7]

In 1917 his only son, Revere, was killed in action in World War I. He was greatly affected by his son's death. Two years later, Osler passed away on December 29, 1919 at Oxford. His wonderful collection of books was bequeathed at his request to his Alma Mater, McGill, where it stands as a monument of his devotion to his profession.

Osler produced a prodigious amount of scientific writings. "His essays on Linacre (1908), An Alabama Student (1908), Servetus (1910), and other subjects are among the most attractive of modern contributions to the history of medicine. In this field he is especially memorable for his studies of the work of earlier American clinicians, whose modern status he has done most to establish. He was the editor of Modern Medicine (1910), also founder and editor of the Quarterly Journal of Medicine (1908)."[8]

Throughout Osler's writings are many pithy aphorisms. These compact, well-turned phrases are widely quoted. "Two conditions . . . are necessary for a man's writings to survive in the form of aphorisms or epigrams — he must be a philosopher with a deep interest in, and understanding of, humankind and he must have the gift of stating simple truths in terse, crisp language. Osler's warm humanity was his own: his philosophy was evolved from long years of thinking and reading and experience: his ability to write from constant practice."[9] Although his writing was done near the turn of the century, his observations are as pertinent today as they were then:

"There are only two sorts of doctors; those who practice with their brains and those who practice with their tongues.

* * * * *

Live a simple and a temperate life, that you may give all your powers to your profession.

* * * * *

Who serve the gods die young — Venus, Bacchus, and Vulcan send in no bills in the seventh decade.

Do not rashly use every new product of which the peripatetic siren sings. Consider what surprising reactions may occur in the laboratory

---

*Part I, Minnesota Med 47:10, Page 1305.

Continued

from the careless mixing of unknown substances. Be as considerate of your patient and yourself as you are of the test-tube.

* * * * *

The practice of medicine is an art, based on science."[10]

* * * * *

"Osler did a great deal of original scientific work, not only in the domain of clinical medicine, but in a number of kindred fields. He was one of the first to describe the blood platelets, and his name will remain associated with the clinical picture of a considerable number of diseases. But the period of his life activities was extraordinarily fruitful to medical science, and among his contemporaries there was an abundance of distinguished clinical investigators. The explanation of Osler's fame is to be found elsewhere. His renown depends upon his personality as physician, as teacher, as man."[11]

Osler himself said in his farewell address to the Johns Hopkins University in 1905: "I desire no other epitaph than the statement that I taught medical students in the wards, as I regard this by far the most useful and important work I have been called upon to do."

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1-5 Published in October issue of Minnesota Med, page 1307.
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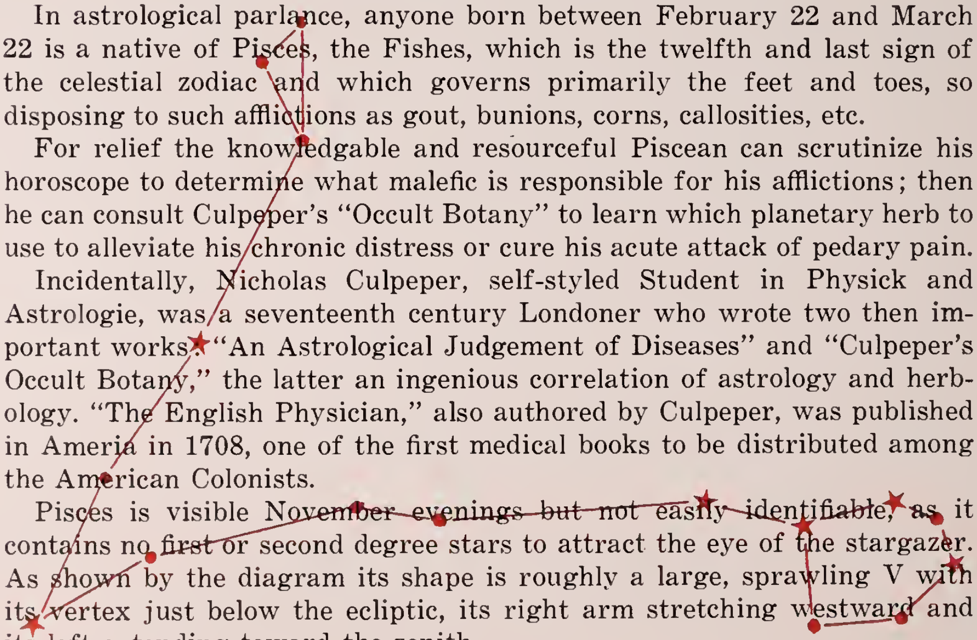
Astrology and Medicine — Pisces, The Fishes

In astrological parlance, anyone born between February 22 and March 22 is a native of Pisces, the Fishes, which is the twelfth and last sign of the celestial zodiac and which governs primarily the feet and toes, so disposing to such afflictions as gout, bunions, corns, callosities, etc.

For relief the knowledgable and resourceful Piscean can scrutinize his horoscope to determine what malefic is responsible for his afflictions; then he can consult Culpeper's "Occult Botany" to learn which planetary herb to use to alleviate his chronic distress or cure his acute attack of pedary pain.

Incidentally, Nicholas Culpeper, self-styled Student in Physick and Astrologie, was a seventeenth century Londoner who wrote two then important works: "An Astrological Judgement of Diseases" and "Culpeper's Occult Botany," the latter an ingenious correlation of astrology and herbology. "The English Physician," also authored by Culpeper, was published in America in 1708, one of the first medical books to be distributed among the American Colonists.

Pisces is visible November evenings but not easily identifiable, as it contains no first or second degree stars to attract the eye of the stargazer. As shown by the diagram its shape is roughly a large, sprawling V with its vertex just below the ecliptic, its right arm stretching westward and its left extending toward the zenith.



Announcing . . . the Second Volume in the New Series from SAUNDERS

Polypoid Lesions of the Gastrointestinal Tract

by Claude E. Welch, M.D.

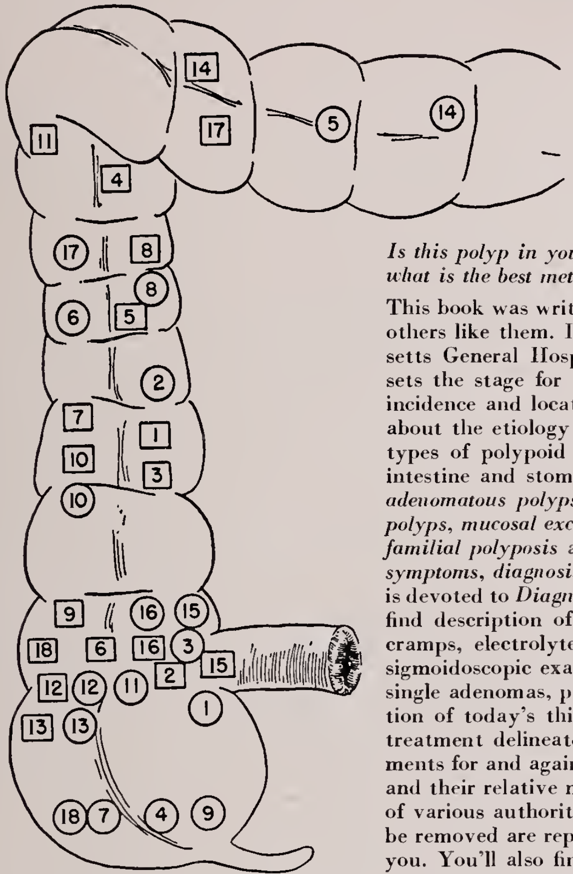


Figure 3-25. *Location of cancer and simple adenomas in resected cancers of the right colon. Squares locate cancers; circles, adenomas.*

Is this polyp in your patient benign or malignant? Should it be removed? If so, what is the best method for this particular lesion in this particular patient?

This book was written to help you answer questions such as those above, and others like them. Its author has drawn on the experience of 1124 Massachusetts General Hospital patients, plus many personal cases. Dr. Welch first sets the stage for a fruitful discussion by defining terms, by discussing the incidence and location of polypoid tumors, and summarizing what is known about the etiology of adenomas. He then proceeds to illuminate the various types of polypoid lesions you'll encounter in the colon and rectum, small intestine and stomach. He describes and illustrates common lesions such as *adenomatous polyps* and *papillary adenomas*, and such rare ones as *pseudopolyps, mucosal excrescences, Peutz-Jeghers polyps*, etc. *Multiple polyposis* and *familial polyposis* are also completely covered. *Etiology, incidence, pathology, symptoms, diagnosis, prognosis, treatment*, are clearly set forth. A full chapter is devoted to *Diagnosis of Polypoid Lesions of the Colon and Rectum*. Here you'll find description of symptoms (bleeding, change in bowel habit, abdominal cramps, electrolyte imbalance, etc.) and physical findings from palpation, sigmoidoscopic examination, and radiologic examination. The relationship of single adenomas, papillary adenomas, and cancer is discussed, with examination of today's thinking on the adenoma-cancer relationship. A chapter on treatment delineates location and identification of polyps, giving you arguments for and against their removal. Polypectomy and resection are discussed and their relative merits contrasted. If resection is decided upon, the opinion of various authorities as to the amount of bowel and mesentery that should be removed are reported. The author states his own conclusions to help guide you. You'll also find helpful consideration of sub-total and total colectomy, extraction of polyps via the anus, posterior proctotomy, resection of the rectum, and sigmoidoscopic removal of polyps.

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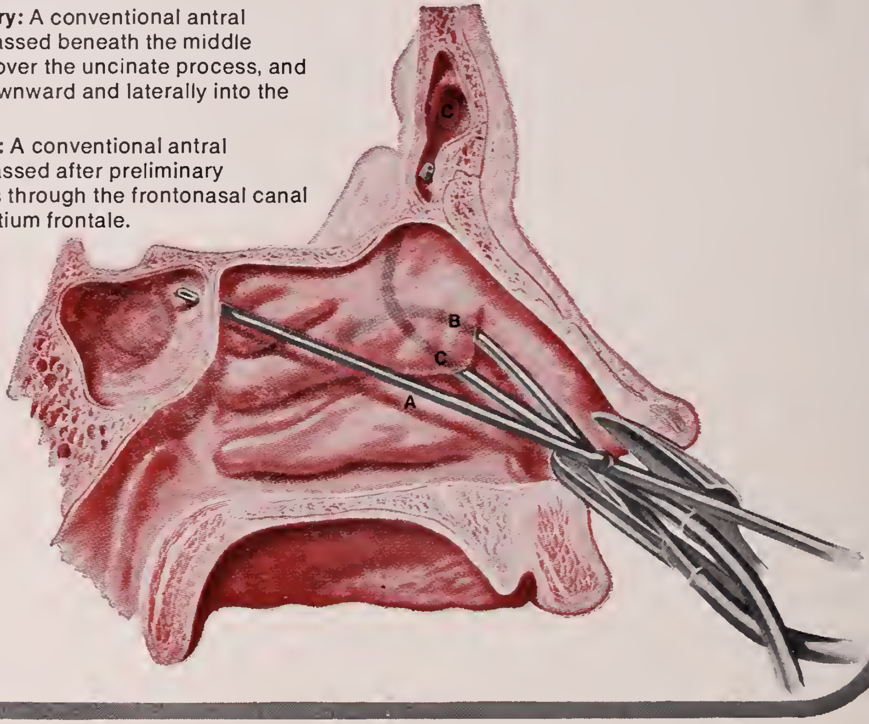

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President's Letter

It must be apparent to all of you who are interested in such things that I am bound to have a feeling of sadness as I prepare this last one of my letters to the members of the Minnesota State Medical Association. Yet those of you who are sympathetically inclined must realize that I have also a feeling of relief in approaching this task. After all, an individual in my position, unless he is completely egocentric, must recognize that he is only a link between the past and the future.

One cannot claim personal credit for any achievement of the Association during his term in office. The foundations for progress were laid one hundred and eleven years ago when a handful of young physicians met in the court house in St. Paul in the Minnesota Territory to organize a medical society which was to become the Minnesota State Medical Association. The elements of progress were added year by year through the efforts of interested and enterprising physicians who learned from the past and envisioned the future. The Association existed long before any of us now connected with it were on the scene and it will continue long after any of us now living are forgotten. Time will continue to add to its strength because of the interest and enterprise of those who will follow us.

I leave feeling that I have left many things undone and unfinished. There is so much that could and possibly should call for attention. It is possible, however, to choose for attention only those things which seem most timely and most important.

My sincere gratitude is extended in behalf of the Association to all those many individuals who have given time and effort in the furtherance of its work. Particular thanks go to Mr. Brunn and his staff for their loyalty and industry. The officers of the Association and members of the Council deserve great credit for their dedication and faithfulness. The Committees have functioned efficiently and wisely.

My personal gratitude goes to the partners with whom I am associated in practice. Without the support of these men and their generosity in providing the time that my duties have required, my office in the Association would have been entirely meaningless.

I shall cherish forever the memories of this year and the honor that you gave me when you chose me as your President.

J. P. Medelman M.D.

J. P. Medelman, M.D.
President
Minnesota State Medical Association

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Dominant Masses and Mammography

J. GERSHON-COHEN, M.D., D.Sc. (Med.)*
ERNEST J. PICK, M.D.*
Philadelphia, Pennsylvania

Mammography is proving useful in the screening of patients for early cancer. Such studies can demonstrate malignant lesions in about 20 per cent of patients without a palpable or dominant breast mass.

CANCER DETECTED before metastasis may be cured by current therapeutic methods. This applies to cancer of the breast as well as to cancer of the skin or cervix. But to treat cancer of the breast after the lesion is detected by the patient, which occurs in more than 95% of all breast cancers, is to forfeit chances of successful therapy in about 50%.

Periodic X-ray examinations of women over 40 years of age can alter this situation. Over the past eight years among some 1,150 women having breast X-ray examinations at six-month intervals, 32 cancers have been discovered so far among 30 patients. Bilateral cancers were found in two women within intervals of less than 18 months. The lesions averaged only slightly more than 1 cm. in diameter, and axillary metastasis was present in only slightly more than 30%, about half the incidence of metastasis now generally encountered.[1] If the eventual mortality statistics of this group become measurably better than those now prevailing, then the value of these periodic breast X-ray studies could be regarded as firmly established. By better mortality statistics, we mean not just increased survival time after therapy, but rather restoration of normal longevity commensurate with healthy women of similar age and circumstances.

Serial Periodic Examinations

A single X-ray study of women over 40 years of age will not suffice. Serial periodic re-examinations are necessary. This would seem to have been demonstrated by a study of some 5,000 women over 40 years of age

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Supported by a grant (CA-09490-07) from the National Institutes of Health, Bethesda, Maryland, and by a grant (T-271) from the American Cancer Society.

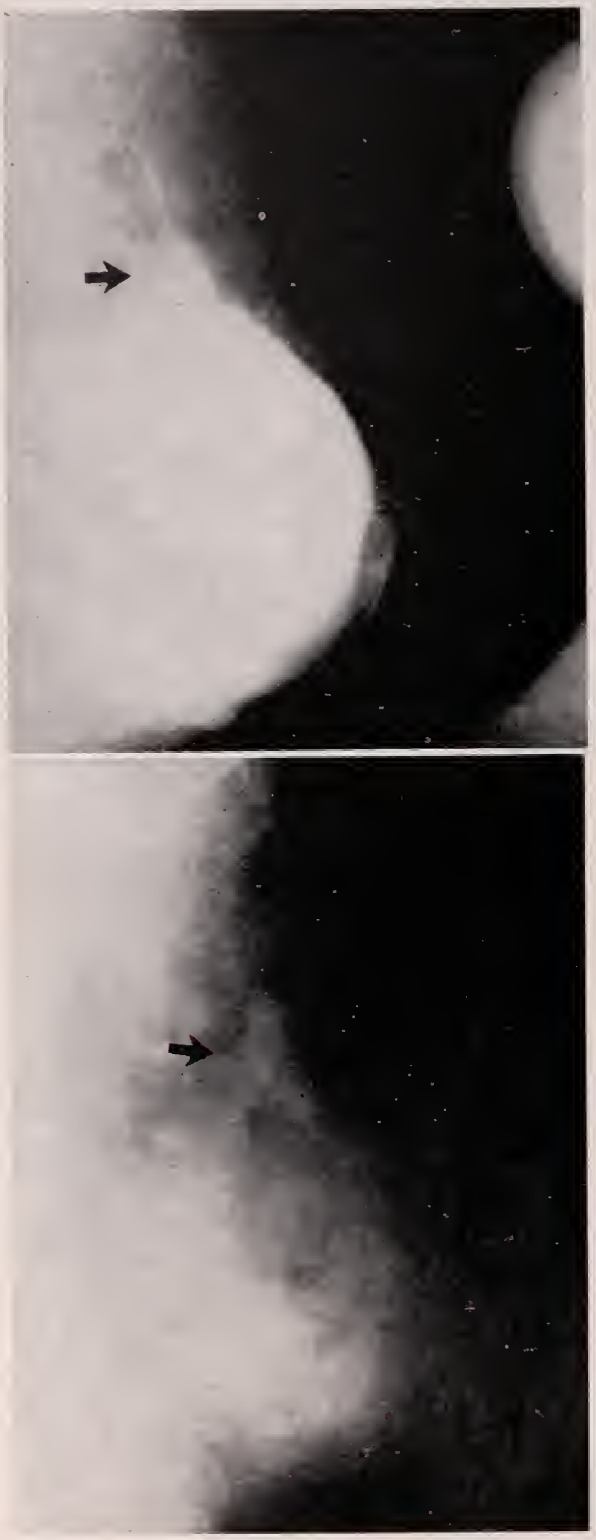

Fig. 1 — Infiltrating duct carcinoma adjacent to a large multilocular cyst. (a-top) Large cyst before evacuation. Small malignant lesion near upper periphery. (b) Malignant lesion more clearly visible after evacuation of cyst. No dominant mass was palpable and surgery was initiated because of X-ray findings.

who had single X-ray examinations of the breasts at the Mayo Clinic.[2] The presence of unsuspected cancer was found in only eight cases, a study which parallels our own experience so far as it goes. By repeated examinations, however, we disclosed an increasing number of patients with cancer, principally by subsequent discovery of lesions missed on the first examination. The reason for this anomaly is the fact that some cancers become evident to the roentgenologist only when he has an opportunity to detect growth of a lesion by the examination of serial films.

The value of routine serial examinations of the breast for the discovery of cancer was also disclosed to us by another experience. Among 102 patients who had postoperative radiotherapy after mastectomy, routine X-ray examinations were made of the remaining breast at six-month intervals. Over a period of seven years, six cancers were uncovered this way, among which axillary metastasis was found in only one case. These same six patients had axillary metastasis in five instances at the time of the initial mastectomy.[3]

Calcium Deposits

Recently when the comparison was made of the surgical and X-ray diagnoses of 500 consecutive cases of breast cancer in our institution, it was found that a positive diagnosis was made by the surgeon in 71% and by the radiologist in 90%. This difference in accuracy stems mostly from the presence of calcium deposits in malignant lesions, which were not palpable.[4] The inference from this analysis is that all patients should routinely have X-ray examinations of their breasts if they have symptoms, regardless of whether or not a dominant mass is present. If surgeons, therefore, were to employ mammography routinely, the combination of the clinical and X-ray findings should result in an accurate diagnosis in better than 95% of all cases; but more important would be inclusion of a larger number of cancers in Stage I among those patients coming to operation. It would follow from this that better mortality statistics could be expected.

The following case reports illustrate how mammography can alter the therapeutic approach in some cases of cancer.

Case Reports

Case No. 1

This 50-year-old patient had been having routine examinations of her breast at six-month intervals since 1956 when she first reported without breast symptoms.

The most recent X-ray examination disclosed a small malignant-looking lesion close to a cyst which had been kept under surveillance for the preceding 2½ years. The surgeon evacuated the cyst, after which he could feel nothing abnormal in the breast. An X-ray re-examination, however, still disclosed what was regarded as a malignant lesion, and the surgeon was again alerted. He consented to do a biopsy in spite of the absence of a palpable tumor, and this disclosed the presence of a small infiltrating duct carcinoma, not associated with metastasis to any of the axillary lymph nodes (Fig. 1a & b).

Case No. 2

This 48-year-old patient was referred for mammography as a check-up procedure. She had no breast complaints, nor was any lesion or mass palpable in either breast.

X-ray examination revealed a small ovoid density in the left breast, containing many minute, punctate calcific particles. The appearance was suggestive of malignancy and was so reported.

Biopsy was undertaken with the aid of X-ray localization because no mass was palpable. An intraductal carcinoma was found with no metastases to the axillary lymph nodes (Fig. 2).

Discussion

The diagnostic possibilities of mammography were first pointed out as far back as 1913 by Salomon.[5] Since then, various roentgenologists at one time or another have confirmed his report; only recently is acceptance of the procedure becoming more evident. The skeptical attitude of surgeons must be held chiefly responsible for this retarded acceptance of mammography in the diagnosis of breast diseases. No one questions the necessity for a confirmed diagnosis by the pathologist in the management of a patient with breast cancer. Though the roentgenologist shares with the surgeon the belief in the validity of this precept, the average surgeon fails to understand the wisdom of preliminary mammography; he fails to appreciate the fact that the roentgenologist will find malignant lesions in about 20% of patients without a palpable or dominant lump. In other words, while the accuracy of palpation and inspection reaches about 70% in the diagnosis of breast cancer, the radiologist can achieve an order of 90%; and when the findings of both the clinician and the radiologist are combined, an accurate diagnosis should be made in more than 95% of all patients with breast cancers regardless of whether or not a dominant lump is present.

Finally, if roentgenography of the breast is used as a screening procedure, even though it entails much energy and expense, cancer of the breast can be found at a time when metastasis to the axillary glands does not exceed 30%: a situation far better than the one which now prevails.

Summary

The routine use of mammography in the diagnosis of all diseases of the breast has proved valuable not only in patients with symptoms, but as a screening technique.

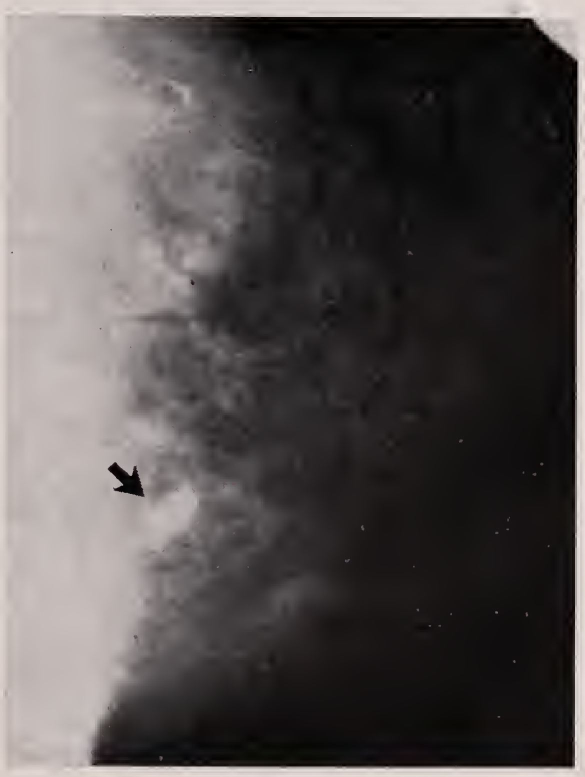

Fig. 2 — Duct carcinoma. Punctate calcifications in a small oval tumor which was not palpable. The surgeon elected to confirm the roentgenologist's suspicion of malignancy. The pathologist found an intraductal carcinoma with no evidence of metastasis to the axillary lymph nodes.

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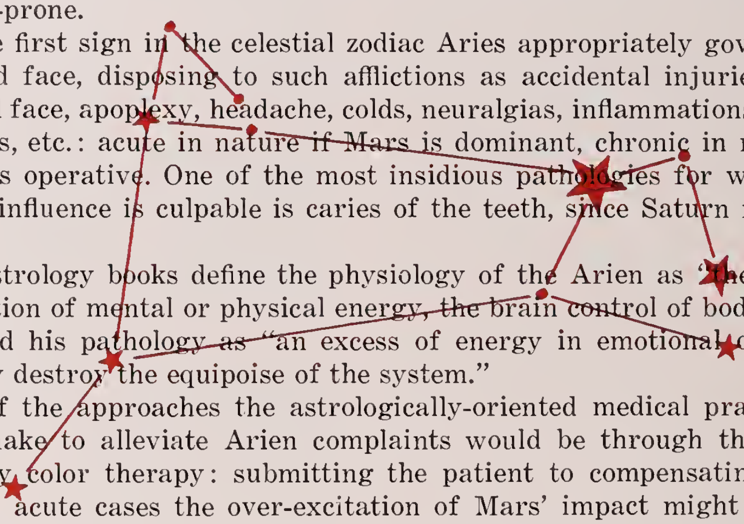
Astrology and Medicine — Aries, The Ram

March 22 to April 22 marks the zodiacal month when the sun resides in the house of Aries, the Ram, identifiable in the southern sky during December by the configuration of the three bright stars that mark the Ram's forehead, neck, and left shoulder.

Astrology alleges that since the ram is an impetuous, butting animal, the native Arien is prone to act rashly and impulsively — making him accident-prone.



As the first sign in the celestial zodiac Aries appropriately governs the head and face, disposing to such afflictions as accidental injuries to the head and face, apoplexy, headache, colds, neuralgias, inflammations, fevers, eruptions, etc.: acute in nature if Mars is dominant, chronic in nature if Saturn is operative. One of the most insidious pathologies for which Saturnian influence is culpable is caries of the teeth, since Saturn rules the bones.

Old astrology books define the physiology of the Arien as "the general distribution of mental or physical energy, the brain control of bodily function" and his pathology as "an excess of energy in emotional outbursts that may destroy the equipoise of the system."

One of the approaches the astrologically-oriented medical practitioner might make to alleviate Arien complaints would be through the use of planetary color therapy: submitting the patient to compensating vibrations. In acute cases the over-excitation of Mars' impact might be mitigated by Saturn's soothing green or Venus' calming blue; conversely to combat the chronicity of Saturnian influence, Martian red or solar orange might be utilized to advantage.

One of the most authoritative references on diseases and planetary colors was Daath's and Raphael's "Medical Astrology," a work undoubtedly now out of print and unavailable to the antiquary.

Pliny's* Treatment for Alopecia

For alopecia Pliny recommended the excreta of animals with honey or bear's grease mixed with laudanum and the plant adiantum.** For defects in the eyebrows he suggested that to the above concoction be added the fungus from the wick of a lamp and the soot found in the nozzle thereof. He also considered that the ashes of animal hoofs mixed with pitch could prevent the hair from falling.

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*See Minnesota Medicine June, 1964, Page 716.
**Maiden hair fern

Search For Truth

The pursuit of truth shall set you free — even if you never catch up with it.

—Roebling Record

Rauwolfia Serpentina and Migraine

H. F. R. PLASS, M.S., M.D.*
Minneapolis, Minnesota

OF FOUR HUNDRED drugs proposed as migraine cures in the past, only half a dozen are now in common use. This indicates among other things, that it is difficult to evaluate the subjective effect of a substance given by a doctor to a patient, as the placebo effect and other factors influence the result. At present, ideal evaluation of drugs requires the method of a double-blind study, though in occasional instances of common diseases long-repeated observations may achieve a measure of validity without this statistical cross-check.

The purpose of this paper is to describe such an instance with Rauwolfia serpentina. Subsequent evaluation by the double-blind method of study may define the position of Rauwolfia in the prevention of common migraine. It seems to have no place in the treatment of the acute attack. Many studies[1-13] have been made of the treatment of the acute attack; but the prophylaxis of migraine will ultimately be the ideal therapy. One discouraging study of prophylaxis with reserpine[14] has appeared.

Classification of Migraine[15]

Classical migraine is the term used to cover the type including aura, whereas *ordinary migraine* is a term used to describe the attack without aura. "Muscle-contraction headache" is used instead of the term "tension-type headache." No diagnoses have changed since starting therapy. All the patients have histories of years of headache and constant therapy. In this sense they serve as their own controls.

Observations

From time to time in the past seven years Rauwolfia serpentina has been prescribed successfully. A review of the charts of patients seen in the past two years is presented in Tables 1 and 2.

Dosage

Rauwolfia has been found useless for attack therapy. For patients in whom it has been useful, it has taken a month before prophylactic value is noted, and when this does occur it seems to be permanent as long as the drug is taken. One hundred milligrams was given to those patients weighing more than 100 pounds, and 50 milligrams to those weighing less than 100 pounds. Medication was taken once daily.

Useless in Muscle Contraction Headaches

Rauwolfia and reserpine were found to be useless in muscle-contraction headaches (tension type). In patients with both hyperten-

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TABLE I
Essential Data for Each Patient in the Study, Including all Failures.

Case	Frequency	Migraine Severity	Tension Type Severity	Duration Of Therapy In Months	Drug	Result
1.	Daily	+++	0	9	Rauw.	95% relief
2.	Daily	+++	0	15	Rauw.	Relief
3.	Daily	++++*	+	12	Res.	Failure-hypertensive, developed depression
4.	Daily	+++**	+	48	Rauw.	85% relief (one/week, mild)
5.	2/wk.	++‡‡	0	6	Rauw.	Relief
6.	Daily	++	++	2	Rauw.	Relief in 2 weeks
7.	Daily	+++	0	1	Rauw.	Relief in 2 weeks
8.	Daily	+++	0	12	Res.	Failure-hypertensive
9.				1	Rauw.	Relief — several 6 mo. attacks previously — now prevented after 3 weeks priming each time
10.	Daily	+++	+	5	Rauw.	Relief
11.	Daily	+++	0	60	Rauw.	Relief
12.	Daily	++	0	4	Rauw.	Relief
13.	Daily	++++	0	84	Rauw.	Relief 90% (occ. Sundays only now)
14.	Daily	++++	0	3	Rauw.	Failure
15.	Daily	+++	0	2	Rauw.	Relief
16.	Daily	+++	0	8	Rauw.	95% relief
17.	Daily	+++	+	2	Rauw.	Failure
18.	2/wk.	+++	0	½ 1957 & 1961	Rauw.	Relief
19.	4/wk.	0	+++	1	Rauw.	Relief
20.	Daily	+++	0	1	Rauw.	Relief, but "too slowed down"
21.	Daily	++	++	12	Rauw.	Relief of headache & hypertension
22.	Daily	++++	0	72	Rauw.	"Very few headaches any more."
23.	Daily	++++	0	11	Rauw.	Relief, except during son's open-heart surgery
24.	3/mo.	++++	++	1	Rauw.	Relief
25.	Daily	+++	0	12	Rauw.	75% relief
26.	Daily to weekly	++++	0	12	Rauw.	50% Relief
27.	Daily	++	0	¼	Res.	No relief — hypertensive
28.	Daily	+++	+++	12	Rauw.	50% relief — chronic aseptic meningitis also
29.	Daily	0	++	6	Rauw.	Failure
30.	Occas.	+++	0	¼	Rauw.	Prevention of prevacation cluster of migraines
31.	3/wk.	+++	0	6	Rauw.	95% relief
32.	Daily	0	+++	2	Rauw.	Failure
33.	Daily	+++	0	84	Rauw.	Prevention of cluster headache and migraine
34.	Daily	0	+++	6	Rauw.	Failure

*4+ Includes aura (classical migraine)
**3+ No aura
‡‡2+ Milder
Rauw. used as abbreviation for Rauwolfia.
Res. used as abbreviation for Reserpine.

sion and migraine, reserpine was found to be ineffective for the migraine portion of their difficulty.

The Result

Benefits

In Table 1 an attempt has been made to estimate the frequency of the headaches, to distinguish muscle-contraction headaches, and to grade migraine and muscle-contraction headaches according to their severity. Only one cluster headache, or histamine headache (Case 33), is listed, and this occurred in an intelligent engineer executive who was able to distinguish it clearly from his daily migraine pattern.

A few cases of muscle-contraction headache are on the list and are included because they were treated with Rauwolfia. One of these was severe, occurred without migraine, and was relieved. This was the only such patient.

An occasional difficulty in evaluation is presented by the remissions which occur spontaneously when the patients' circumstances change for the better. One such exception concerns the patient who used therapy successfully before all vacations and discontinued it after the vacation had begun.

Failures

Table 2 analyzes failures and shows that reserpine did not effectively prevent headache. This may be because Rauwolfia contains other substances in addition to reserpine. Pure tension-type or muscle-contraction headaches were not helped in two cases; but one such headache is shown to be benefitted in Table 1. In the total group of patients, 27 per cent were not relieved by either of the drugs. When one considers only the 25 patients with classical and ordinary migraine who were treated with Rauwolfia serpentina, 16 per cent (four patients) were not benefitted. Patients reporting only 50 per cent relief are listed as failures.

Discussion

The data suggest that of the 19 alkaloids, other than reserpine in Rauwolfia serpentina, one or more may prevent migraine headaches if the migraine is typical. A two to four-week priming period of daily medication seemed to be required before benefit was obtained. One patient observed a feeling of being too slowed down and discontinued the medication because of this, although the headache was relieved. A few patients had minor stuffy noses, but only temporarily. No depression occurred from Rauwolfia. Only four patients failed to obtain prophylactic relief when Rauwolfia serpentina was administered daily in small doses for a period of a month or more. Relief failed to occur in some patients until one month of treatment; but once prophylaxis occurred, it continued as long as the drug was taken. No benefit was seen in treating the acute attack. Also no benefit was observed from the use of reserpine in hypertensives who had migraine; likewise there was no benefit in two of the three muscle-contraction headache patients.

TABLE 2

Analysis of Failure and 50% Relief

C.T.:	Classic Migraine	Rauwolfia — No explanation of 50% relief
S.K.:	Ordinary Migraine plus Tension-Type (plus meningeal irritation)	Rauwolfia — 50% relief 1 year, now 1 year 100% relief
M.F.:	Classic Migraine	Rauwolfia — "Impossible home situation"
C.J.:	Ordinary Migraine plus Tension-Type	Rauwolfia — Only 2-week trial of therapy
B.M.:	Tension-Type Headache	Rauwolfia — No relief in 6 months
J.D.:	Tension-Type Headache	Rouwolfia — No relief in 2 months
R.B.:	Classic Migraine, Hypertensive (72-yr.-old lifetime migraine recluse)	Reserpine — 2 months, depression
K.B.:	Ordinary Migraine, Hypertensive	Reserpine — Over 1 year
P.U.:	Ordinary Migraine, Hypertensive	Reserpine — 1 week use only

All failures are shown, including those treated with Reserpine, tension-type headache (muscle-contraction type), and Rauwolfia-treated migraine which failed to yield.

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WHAT'S YOUR DIAGNOSIS?

After a fire broke out in the mines at Idria near Trieste, about 900 persons became ill. One described the first symptom as unsteadiness of the arms, succeeded by quivering of the muscles, which progressed slowly, with the muscle activity becoming almost convulsive. The tremulous hand could no longer be directed with precision, so that after a time he could scarcely convey food to his mouth. Later the legs began to shake, and the knees were also so affected that in walking they trembled and danced about almost as if they were hung on wire. Speech was hurried, with staccato and stammering, and as the condition progressed there seemed to be a disturbance of the intellect. In addition there was loss of appetite and obstipation.

Physical examination revealed salivation, inflamed and unhealthy gums, and swelling of the tongue. The salivary glands were enlarged and painful. The patient was weak and listless. No other physical findings were recorded.

What's Your Diagnosis? Turn to page 1474.

It is unfortunate that so many citizens are demanding something for nothing. It is even more unfortunate that they are getting it.—Grit

When they come downstairs from their Ivory Towers, Idealists are apt to walk straight into the gutter. — Logan Smith

Mercury Intoxication and the Nephrotic Syndrome

*A Report of Three Cases in One Family**

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ALTHOUGH POISONING by mercury vapor occurs almost exclusively in industry, we have recently observed three cases in a family of ten, resulting in the nephrotic syndrome. The members of this family were exposed to mercury vapor in their home for four months. The mother, an 11-year-old daughter, and a 2½-year-old son were hospitalized with this syndrome. Two and one half weeks later it was learned that in August 1963, the father had brought home a five-pound jug of metallic mercury, and allowed the children to use it to polish coins. Mercury was spilled on the asphalt tile floor and living room rug, and polished coins were frequently scattered on the rug. The mother gathered up spilled mercury and coins with her hands. Gross contamination of the rug with metallic mercury resulted in a large evaporation area. Significant quantities of mercury were found in the urine of the mother and the two children who were hospitalized. Urine from the remaining asymptomatic members of the family also showed mercury (Table 1).

The threshold value for industrial exposure to mercury vapor in air is 0.1 mg. per cubic meter, based on 40 hours per week exposure. Mercury levels in the home of our patients were as high as 2.35 mg./cu. m., the highest concentrations being measured close to the living room rug in spots where mercury had been spilled. After removal of the rug the room air-mercury concentration was markedly reduced and no further disease occurred in the family.

TABLE I**
Urine Mercury Determinations — mg./liter.

Patient With Nephrotic Syndrome	Level	Asymptomatic Members of the Family	Level
Case 1	.22	1	.08
Case 2	.11	2	.18
Case 3	.42	3	.07
		4	.13
		5	.03
		6	.04
		7	.38

**All were exposed to room air concentrations of mercury as high as 2.35 mg./cubic meter for four months. Maximum allowable concentration for industrial mercury exposure is 0.1 mgm./cubic meter.

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Report of Cases

Case No. 1

A 10-year-old white girl, was admitted to the hospital November 14, 1963, because of swelling of the face and legs — of three days' duration. There was no history of antecedent illness. Her weight had increased from 72 to 88 pounds in the preceding few weeks.

Examination revealed marked pitting edema of the face, legs, and ankles. The blood pressure was 92 64 mm. Hg. The remainder of the examination was normal. The laboratory data are summarized in Table 2.

Triamcinolone, 16 mg. daily, was begun three days after admission. Oral penicillin and hydrochlorothiazide, 50 mg. daily, were also given. Three weeks later dimercaprol (British Anti-Lewisite) was begun. Treatment resulted in complete remission with a 20-pound diuresis.

Case No. 2

A two-year-old brother of the first patient, was admitted November 29, 1963, because of swelling of the face, eyes, arms and legs — of sudden onset the previous day.

Examination revealed marked periorbital and facial edema, and scrotal and leg edema. On the day following admission, triamcinolone 16 mg. daily was started, and one week later dimercaprol with a total dosage of 250 mg. was begun. The dosage of triamcinolone was then gradually reduced to 2 mg. daily, and the patient was discharged. The total weight loss was seven pounds. Reduction of edema became apparent on the third day after admission and had completely subsided by the time of discharge on the 22nd day. The patient has since remained asymptomatic.

Case No. 3

The 31-year-old mother of the other two patients, was admitted to the hospital November 15, 1963, complaining of swelling of the legs, fatigue, and fullness of the abdomen — of one week's duration. The abdomen was full, but evidence of ascites could not be elicited. There was grade III pitting edema of the feet and legs.

Treatment consisting of a low-sodium, high protein diet, cholorathiazide, and spironolactone was ineffective. Three weeks after admission the patient was given a five-day course of dimercaprol in a total dosage of 1800 mg. Methylpredisolone 16 mg. daily was begun two weeks later, gradually increased to 48 mg. daily, and then gradually tapered to 12 mg. daily. Diuresis began on the 43rd day of hospitalization, with a weight loss of 35 pounds. Albuminuria disappeared and the patient was discharged.

On February 17, 1964, the patient was readmitted to the hospital for seven days, following a mild upper respiratory infection coincident with omission of methylpredisolone. She had gained weight with albuminuria recurring two weeks before admission. Adrenal steroid treatment resulted in prompt remission.

Discussion

Chronic mercury poisoning causes renal tubular degeneration.[1] Mercuric ion has a specific affinity for sulfhydryl groups and precipitates intracellular protein, with toxicity varying in direct proportion to the degree of ionization. Mercury bichloride, with a high degree of ionization, is acutely corrosive to the gastrointestinal mucosa and produces profound damage to the renal tubule. Metallic mercury is relatively innocuous in the intestinal tract and is slowly absorbed through the skin; but it is highly toxic when rapidly absorbed through the lungs as mercury vapor. Shortly after absorption, the ionized salts are deposited in the kidneys, liver, spleen, intestinal wall, heart, muscles, lungs, brain and bones in decreasing order of concentration. Excretion begins promptly and is largely completed in six days, although traces of mercury may remain in the tissues for many months. Therapy with dimercaprol, which has a greater affinity for the mercuric ion than the sulfhydryl groups, should be begun as promptly as possible,[1] with a dosage of 3.0

TABLE 2

Laboratory Data in Patients with the Nephrotic Syndrome Following Exposure to Mercury.

Case Number	Age (Years)	Date	Weight Pounds	Serum Albumin	Proteins-Gm./100cc. Globulin	Serum Cholesterol mg./100cc.	Urine Albumin
1	10	11/14/63*	88	0.7	2.9	782	++++
		12/14/63†	68	2.8	3.2	350	0
2	2	11/29/63*	43	1.0	4.3	712	++++
		12/22/63†	36	3.6	3.5	398	0
3	31	11/15/63*	170	1.4	2.2	800	++++
		1/ 3/64†	135	2.4	3.3	180	0

*Before treatment.

†After treatment with dimercaprol and adrenal steroids.

mg. per kg. every twelve hours. In severe poisoning the recommended dosage is 5 mg. per kg. initially, followed by 2.5 mg. per kg. every three hours during the first 24 hours.

Edwards[2] found that the toxic effects of mercury on the kidney were virtually limited to the proximal convoluted tubules and that glomerular changes were slight. Becker, Maher and Scheiner,[3] however, reported five patients with the nephrotic syndrome secondary to mercury. Three patients had been exposed to ammoniated mercury in the treatment of psoriasis; one had been exposed to a paint additive containing mercury; and one had taken a mercurial diuretic 36 mg. daily for two years. Renal biopsies of these patients demonstrated membranous glomerulonephritis. Treatment with adrenal steroids was effective.

Worthen, Vernier and Good[4] reported a seven-month-old infant who developed the nephrotic syndrome following exposure to a diaper rinse containing mercury bichloride. The urine excretion of mercury in this patient was 27 micrograms per day. Following withdrawal from exposure to mercury and corticotropin therapy, the patient recovered completely.

During an investigation of Pink Disease (Achrodynia), Wilson and co-workers[5] found five nephrotic patients who excreted large amounts of mercury. Four responded to dimercaprol and the fifth died before treatment could be started. Steroids were not given.

Other mercurial compounds such as teething powders, vermifuges and ointments have also been reported to produce albuminuria and the nephrotic syndrome. These patients usually show clinical recovery coincident with the disappearance of mercury from the urine. In industrial exposure to mercury, proteinuria and the nephrotic syndrome disappeared when the workers were removed from contact with mercury.[6]

In this family of ten, all exposed to mercury vapor and all showing mercury in the urine, only three members developed the nephrotic syndrome. Similarly in factories where many workers are exposed to mercury and found to excrete mercury in the urine, all are not equally affected.[6] The paucity of reported cases of the nephrotic syndrome occurring in patients exposed to mercury suggests that this is an allergic response. The effectiveness of adrenal steroid therapy in these patients also supports this hypothesis.

Summary

Three patients in a family of ten developed the nephrotic syndrome after being exposed to mercury vapor in their home for four months. All recovered after treatment with dimercaprol and adrenal steroids. Mercury poisoning should be suspected in patients with the nephrotic syndrome. The most useful laboratory test is the urinary excretion of mercury.

Acknowledgment

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If you cannot help worrying, remember that worrying cannot help you either.
—Wesleyan Christian Advocate

Histoplasmosis

• *Involving*
• *the*
• *Adrenal*
• *Gland*

HISTOPLASMA CAPSULATUM has been known for many years to be the fungus that has the greatest predilection for the adrenal glands,[1,2] a finding which was supported by our previous study.[3] Of 62 necropsy cases of mycotic infections, eight were cases of histoplasmosis, and the adrenal glands were involved in all eight. In four of these eight cases there was evidence of thrombosis of the central adrenal vein, which was bilateral in one case. This finding, which hitherto appears to be unreported in the literature, is the basis for this report.

Epidemiologic Features

Histoplasmosis is now recognized as a common fungus disease that is systemic in nature and has its principal manifestations in the lungs and reticuloendothelial system.[4,5] Although histoplasmosis is usually benign, it may result in a lethal process. It is frequently an imitator, especially of tuberculosis.

Most of the cases of histoplasmosis have been reported in the United States. From the results of the histoplasmin skin test, perhaps 20 per cent of the population of the United States has been infected with H. capsulatum; in endemic areas 70 to 85 per cent of the population have had a primary infection.

Contagion

The disease is not contagious in the sense that it is spread from man to man or from man to animal; the infection is airborne or spread by inoculation. Most infections appear to result from inhalation of contaminated dust; the organism has been isolated from soil, caves, and the dung of the pigeon, chicken, and bat. Cleaning a chicken coop, silo or barn or visiting a cave or excavation may be important in the patient's history. H. capsulatum exists as a saprophyte in the mycelial form in soils, thick accumulations of matted manure, and the like. Resistant spores are produced which are inhaled in the contaminated dust and which can be found in the smaller bronchioles and alveoli of the lung. After entry into the body is accomplished, however, the spore is converted to the yeast phase. The factors involved in this conversion, which takes place at body temperature, are not known. In the yeast form,

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Acute Hemorrhagic Infarction

TABLE
Blood Vessel Involvement in Histoplasmosis: Comparison With Degree of Anatomic Destruction and Clinical Severity (Including Addison's Disease)

Case	Parenchymal infection	Vascular pathology	Destruction, grade‡		Addison's disease
			Right	Left	
1	Scant granulomata	None	0	0	Suggestive
2	Widespread necrosis	Central adrenal vein not recognized; areas of focal necrosis in cortex	4	4	—
3	Extensive caseous granulomata and diffuse fibrosis	Left adrenal, thrombosis of central adrenal vein and areas of hemorrhage and infarction	3	3	Suggestive
4	Multiple granulomata, widespread destruction of adrenal tissue	None	4	3	Suggestive
5	Extensive caseous granulomata	Right adrenal, thrombosis of central adrenal vein and area of recent hemorrhage	3	3	Probable
6	Scant granulomata	Right adrenal, thrombosis of central adrenal vein	0	0	Suggestive
7	Scant granulomata	No thrombosis but infarcts in one gland	0	0	—
8	Scant granulomata	Infarcts and thrombosis of adrenal veins in both glands	0	0	—

‡Basis of grades 0 to 4 with increasing severity based on per cent of viable adrenal tissue remaining.

H. capsulatum is essentially an intracellular parasite that multiplies mainly in reticuloendothelial cells.

Clinical Syndromes

After the spore has been inhaled, the resulting respiratory infection may be subclinical, mild, or severe, and may simulate any viral or bacterial pneumonitis.

Acute Pulmonary Disease

The acute pulmonary forms are the most common. In the large majority of cases, however, the initial infection is undiagnosed because of the flu-like nature of the illness and because many patients fail to seek medical advice. Such forms of the disease are usually benign and rarely fatal, and the pulmonary lesions usually undergo complete resolution or heal by calcification. Rounded lesions (coin lesions) that result from the primary infection later may be confused with neoplasms.

Chronic Pulmonary Disease

In some patients, fibrocaseous lesions develop with cavity formation. Chronic pulmonary infection is less benign than initial or primary histoplasmosis, and the prognosis is poor in the untreated case. Chronic pulmonary histoplasmosis usually has a slowly progressive course with increasing debility and ultimate pulmonary fibrosis or cor pulmonale. H. capsulatum often can be cultured from the sputum. This type of disease is seen sometimes in patients in tuberculosis sanatoriums, since it can be misdiagnosed easily as pulmonary tuberculosis.

Chronic Disseminated Histoplasmosis

Disseminated histoplasmosis may be subdivided into benign and progressive forms; the former has a good prognosis; the latter is nearly always fatal. The chronic disseminated form occurs mainly in older persons and, like chronic pulmonary histoplasmosis, frequently is fatal. Whereas two thirds of the patients with chronic pulmonary disease are more than 40 years old, about one third of those with chronic disseminated disease are children less than 10 years. In chronic disseminated histoplasmosis, which represents less than 1 per cent of the cases, ulcers of the tongue, pharynx, larynx, and nose may be mistaken for carcinoma. Disseminated disease develops before death in perhaps 5 per cent of the patients who have the chronic pulmonary disease. Significantly, about half of the patients with chronic disseminated disease have coexistent pulmonary involvement; miliary lesions and more localized changes may be noted on roentgenograms of the thorax. In chronic disseminated disease, intestinal lymphoid tissue also may be involved, the ulceration of which may cause gastrointestinal bleeding; cervical lymphadenopathy may simulate lymphoma. With disseminated infection of the reticuloendothelial system, the classic picture is that of fever, emaciation, hepatosplenomegaly, lymphadenopathy, and depression of the marrow; purpuric manifestations may occur, especially in children. Some of these cases present as hypersplenism. That Addison's disease occurs in some of these cases was a stimulus to the present investigation. A case of pericardial effusion due to histoplasmosis, in which the histoplasmin skin reaction was negative and the histoplasmin complement-fixation reaction was repeatedly negative, has been presented.[4] Although the mortality rate in disseminated histoplasmosis has been high, a benign nature (acute benign dissemination) may be indicated by the high rate of splenic calcification in relatively resistant individuals who live in known endemic areas.

Histoplasmosis is rarely confined to the skin or to the central nervous system.

Diagnosis

Diagnosis of histoplasmosis depends almost solely on demonstrating organisms in body fluids or tissues. The small oval fungus may be seen in phagocytic cells of the blood, marrow, liver, and spleen. In order to grow the organism, one must be persistent; sputum and gastric samples, bronchoscopic aspirations with saline washings, blood, marrow, and biopsied material such as glands and lung tissue may have to be cultured and recultured. Precipitin and complement-fixation reactions, when positive, alert one to the possibility of active disease. Such serologic response to infection usually appears during the third to the sixth week of the disease. A positive skin reaction may alert one to the possible presence of histoplasmosis in a given case; but, contradistinctly in endemic regions, this may prove confusing, since most of the population will have positive reactions. Also, the skin test may give a negative reaction in up to 20 per cent of the patients who have chronic pulmonary disease and in an even higher percentage of those who have disseminated disease.

Therapeutic Considerations

Most of the patients with acute forms of histoplasmosis, which are benign and usually unrecognized, require no specific therapy. Institution of therapy on the basis of a positive skin reaction to histoplasmin alone is not justified. When treatment is warranted, a balanced medical and surgical approach usually is considered. Medical management of the disease resembles that of pulmonary tuberculosis.

Amphotericin B is effective in some cases of histoplasmosis. The antibiotic is administered intravenously for systemic disease, and its use requires careful supervision. Amphotericin B may suppress and halt progression of the disease and allow surgical extirpation of residual lesions.[2] Thus far, it appears that the mortality rate from disseminated disease has been reduced to about 25 per cent among patients who have received amphotericin B; in chronic pulmonary histoplasmosis the mortality rate among the adequately treated group is only about half that of the untreated group. While current management of histoplasmosis is far from completely satisfactory, considerable progress has been made in the recognition and therapy of the disease during the last half century.

Pathogenesis

Localization Versus Dissemination

Factors, as yet not fully understood, determine the localization or dissemination of the infection. The tissue response to the organism is the formation of a granuloma, generally indistinguishable from other granulomata. The reason is usually not evident why infection remains localized to the lungs with formation of a granulomatous lesion and subsequent calcification in one patient and yet, in another, spreads by way of the lymph and blood streams to various other organs.

Concept of Adrenal Involvement

Of 566 cases of Addison's disease encountered from 1900 through 1929, 60 per cent were considered to be tuberculous in origin and none were diagnosed as representing histoplasmosis.[6] From 1939 to 1940, 21 cases of histoplasmosis with the involvement of the adrenals were reported.[7] A case report in 1940 showed involvement of the left adrenal.[8] Thirteen additional cases of histoplasmosis were reported in 1940; apparently adrenal insufficiency was the cause of death in all of them.[9] Ziegler,[10] on reviewing the literature to 1945, reported adrenal involvement in 21 of 79 cases of histoplasmosis found. In 1948 Rawson and associates[1] described 19 cases. In 17 of these the adrenals were involved; in nine of the 17, there was massive necrosis with symptoms of adrenal insufficiency. In 1954, Vivian and co-workers[2] reviewed 20 cases of disseminated histoplasmosis both histopathologically and clinically, and found adrenal involvement in six.

In 1956 Crispell and associates,[11] reviewed the cases of Addison's disease associated with histoplasmosis and added four. Interestingly, in these added cases, three out of the four patients had oral lesions. Of 103 cases reviewed, 36 (35 per cent) had adrenal involvement, and fifteen of the 36 had symptoms suggestive of adrenal insufficiency. One of these had an addisonian crisis postoperatively, which responded to intravenously-administered hydrocortisone. The pathologic findings in the one case described indicated extensive caseous necrosis of the adrenal glands, but involvement of vessels was not mentioned.

In a review[12] of 100 consecutively hospitalized patients who had histoplasmosis, it was emphasized that most deaths were due to adrenal involvement with production of adrenal insufficiency.

In one of the latest reviews[13] of cases of disseminated histoplasmosis, the adrenals were involved in 14 (82 per cent), and in five of these, adrenal insufficiency had developed. No mention was made of changes in the adrenal blood vessels.

Singular Characteristics in Adrenal Involvement

Tissue response to H. capsulatum in the adrenals tends to be of a more extensively necrotic nature than in other organs of the body.[13-16] Epithelioid and giant cell reactions and fibrosis are minimal and, when present, are usually in areas where adrenocortical cells have been destroyed. The factors responsible for the difference in the inflammatory response in the adrenals in contrast to other areas have not been completely elucidated, but Frenkel[17] has described data that may be pertinent. He has shown that the administration of corticotropin (ACTH) apparently accentuates adrenal function and necrosis and decreases the granulomatous reaction.

Present Series

In each of the eight cases of histoplasmosis with involvement of the adrenal gland in our series, the diagnosis was confirmed by both culture and microscopic identification of the organism in the adrenal gland (Table). In addition, in each case, the disease was disseminated throughout the body.

Stains Employed

The histochemical stains employed included hematoxylin and eosin, azure eosin (pH 4.5), silver chromate, Gram, periodic acid-Schiff (PAS), and acid-fast stains. The elastic van Gieson and Mallory-Heidenhain stains were used to delineate blood-vessel involvement.

Attention has been drawn in recent years to variations in the morphologic appearance of the fungus when it exists extracellularly in necrotic tissue.[14] The poor staining of the organism by the hematoxylin and eosin stain and the distorted and large forms occasionally associated with hyphae formation have been emphasized. The periodic acid-Schiff stain, which is commonly referred to in discussions of H. capsulatum in the literature, stains the capsule, whereas it leaves the body unstained or faintly stained. In contradistinction, silver chromate primarily colors the central part of the organism black but leaves the capsule unstained (Fig. 1a and b).

Patients

The ages of the patients ranged from seven months to 77 years. Except for one patient from California, all were from Midwestern states. The degree of clinical severity of the disease varied considerably, but it followed a rather fulminating course in all patients. Two had oral lesions; these have been emphasized in the past as an ominous sign. Only one of the eight patients had laboratory evidence that indicated probable adrenal insufficiency; four additional patients had symptoms suggestive of adrenal insufficiency.

Patients who were considered as having probable or suggestive adrenal insufficiency were those in whom the clinical or laboratory data included one or more findings compatible with Addison's disease. Of the four patients considered to have suggestive adrenal insufficiency, one (Case 1, Table) had a decrease in blood pressure to 90 mm. of mercury systolic and 60 mm. diastolic, while the concentration of sodium in serum measured 120 mEq. per liter (normal, 135 to 145 mEq. per liter); and the concentration of potassium in serum measured 5.5 mEq. per liter (normal, 4.0 to 5.0 mEq. per liter). In Case 3, the concentration of sodium in serum was 110 mEq., that of potassium in serum 6.7 mEq., and that of chlorides in serum 84.6 mEq. per liter. One patient (Case 4) exhibited diffuse brown pigmentation and profound weakness, and vomited preterminally. One patient (Case 6) was well tanned and had nausea, vomiting, and abdominal pain. In the patient considered to have probable adrenal insufficiency (Case 5), the result of the Kepler-Power-Robinson water-loading test had been positive. When shock had followed bronchoscopy, the response was good to cortisone administered intramuscularly. The normal concentration of the serum electrolytes and the steroids in the blood and urine presumably reflected the exogenous cortisone. Admittedly, some of these findings were nonspecific and, therefore, cannot be interpreted as strong evidence for any degree of adrenal failure; but to ignore these findings might lead one to assume that adrenal function must have been normal.

In contrast to the other patients in our series who had actinomycosis, nocardiosis, or cryptococcosis, five of the eight patients who had histoplasmosis had bilateral adrenal involvement; in four, the degree of adrenal destruction exceeded 90 per cent. In four of the eight, there was evidence of thrombosis of the central adrenal vein, which was bilateral in one case (Fig. 1b to 2b). Three of the four patients who had suggestive clinical evidence of adrenal failure and the one patient who probably had adrenal insufficiency demonstrated the vascular lesion. In two of these with pathologic changes in the blood vessels, the disease had been clinically fulminating.

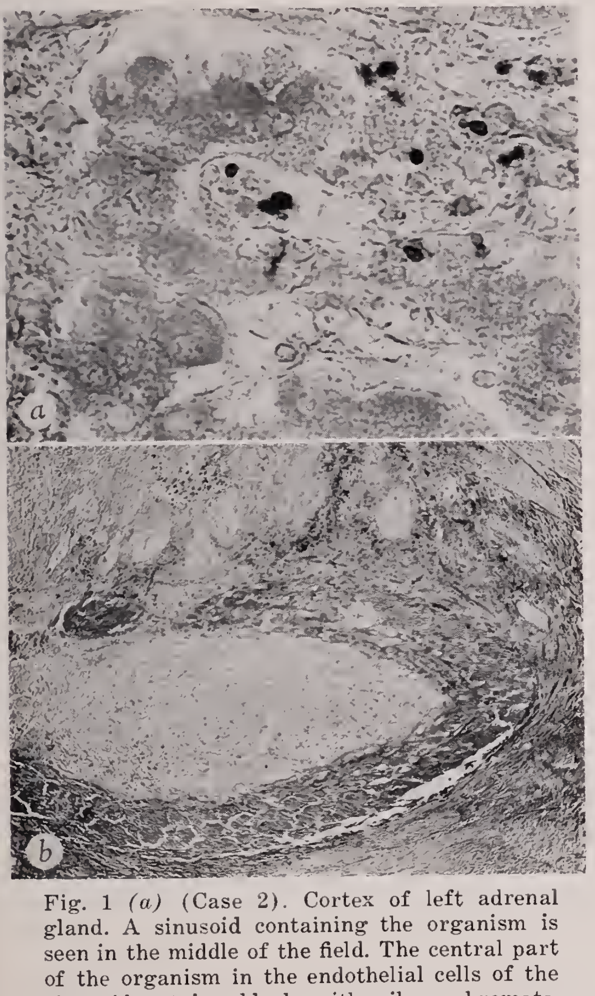

Fig. 1 *(a)* (Case 2). Cortex of left adrenal gland. A sinusoid containing the organism is seen in the middle of the field. The central part of the organism in the endothelial cells of the sinusoids stains black with silver chromate. The capsule is not apparent and is unstained. Grade 4 destruction (silver chromate; reduced from x880). *(b)* (Case 3). Medulla of left adrenal gland. The central adrenal vein is completely occluded by a thrombus. Organisms are seen within the lumen, the wall, and the adventitial layers of the vein (silver chromate; reduced from x25).

Pathologic Findings

The gross appearance of the adrenals varied widely depending on the degree of parenchymal involvement and destruction. In one patient, both adrenals appeared normal, while, in two other patients, one adrenal in each was normal, the other gland showing only a few scattered granulomata. In the remaining five patients, the adrenals were either markedly enlarged with numerous yellowish necrotic areas of caseation or were completely replaced by a necrotic amorphous mass. In two patients, the adrenals showed hemorrhagic areas which were verified microscopically as infarcted areas with surrounding hemorrhage (Fig. 1b to 2b).

The histologic appearance varied from that of well-circumscribed granulomata to that of extensive caseation destruction. In the patients who showed definite granulomata, a surrounding cellular reaction was usually present and consisted of lymphocytes, giant cells, and phagocytes with areas of fibrous tissue. In all cases, the typical organisms were seen in the parenchyma, especially in the phagocytic cells. In some of the cases, the endothelium of capillaries and sinusoids contained the organism (Fig. 1). Inflammatory lesions of the walls of larger adrenal veins and thrombosis of the central adrenal vein associated with areas of hemorrhage were seen in four of the eight cases (Fig. 1b, 2a, and b).

Comment

The pathogenesis of adrenal involvement by H. capsulatum can only be postulated in the light of present knowledge. Primary involvement of the adrenal parenchyma may be by way of organisms phagocytosed by adrenal-reticuloendothelial sinusoidal cells (Fig. 1a). The walls of larger adrenal veins may be involved: (1) via the bloodstream following phagocytosis of organisms by the vessel endothelium (luminal route) or (2) by direct extension from granulomata adjacent to the adventitial layers of the vein (mural route, Fig. 1b).

It seems possible that sudden cessation of adrenal venous return by thrombosis of the central adrenal vein and infarction may have been responsible for relatively acute terminal clinical phenomena in patients with histoplasmosis of the adrenals, in contrast to any manifestations of the more chronic-appearing granulomata. This hypothesis may be exemplified best in Case 5 in which there was laboratory evidence of probable adrenal failure. The clinical course of the disease had been chronic; but death was sudden, and, at necrospy, vascular pathologic changes were evident. The serum electrolytes and steroid determinations had been normal two days before the patient's demise. Possibly the patient had had compensated adrenal insufficiency until the adrenal infarction occurred, at which time most of the remaining functional adrenal tissue was destroyed.

Frenkel,[17] in discussing the pathogenesis of adrenal failure, introduced some interesting aspects of adrenal pathology which may contribute to the explanation that certain glands are prone to develop acute lesions. He suggested that, as the gland is progressively involved by the mycotic process, the output of adrenal steroids decrease correspondingly. The lowering of the plasma cortisols would tend to enhance release of corticotropin (adrenocorticotropic hormone) by the pituitary. The remaining intact adrenal cells under the stimulating effect of adrenocorticotropic hormone tend to hypertrophy. Adrenal glands under these conditions appear to be more dependent on the integrity of their vascular supply than the gland that is not subjected to such hyperstimulation. A major vascular thrombosis in such a gland may be more likely to eventuate in acute deprivation of functioning adrenal tissue, and hence in sudden demise of the subject.

One might wonder why there was not a better correlation between the clinical evidence of adrenal failure in the cases in our series and the degree of anatomic destruction of the glands. Perhaps this can be explained in part by other factors that contribute to the clinical syndrome of adrenal insufficiency. The supply of salt, the amount of stress, and the effects of other unidentified factors as well as the degree of destruction of the glands may modify the clinical course and laboratory findings.

Summary

The study consists of eight cases of histoplasmosis in which necropsy data were available. Addison's disease was suggested by the

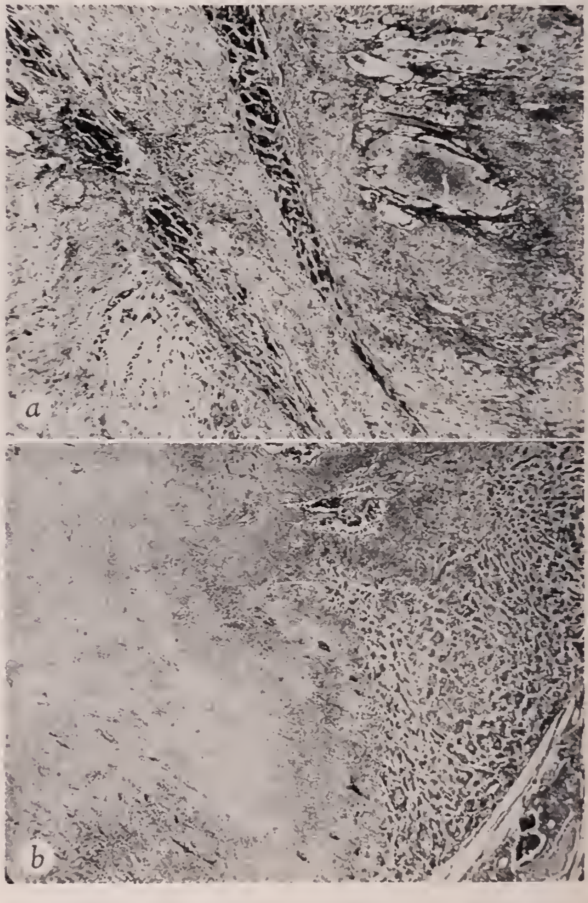

Fig. 2*(a)* (Case 3). To the right of occluded vein is a hemorrhagic infarct. In the left lower field is an area of phlebitis near several granulomatous foci (azure eosin; reduced from x25). *(b)* Cortex of left adrenal gland. On the right there is normal adrenal tisue. On the left there is evidence of recent infarction, focal hemorrhage, and congested vessels (azure eosin; reduced from x25).

clinical findings in four, and adrenal insufficiency by the laboratory data in one. Involvement of the adrenal glands was found at necropsy in all eight cases. There were two distinct types of lesions, the caseous granuloma and hemorrhagic infarct. Thrombosis of the central adrenal vein associated with areas of hemorrhage was seen in four of the cases in which the clinical findings indicated adrenal disease.

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BESNIER-BOECK-SCHAUMANN SYNDROME

(Boeck's sarcoid; sarcoidosis)

This is a generalized systemic condition most frequently affecting lymph nodes, skin, lungs, spleen, liver, salivary glands, and eyes. The greatest incidence is in the third and fourth decades and it occurs more frequently in Negroes.

There are as a rule no severe constitutional symptoms, but there is a lack of energy and undue fatigue. There may be malaise and fever. The presenting symptoms usually relate to involvement of the lungs, mediastinal lymph nodes, and superficial lymph nodes or skin. The lesions may be widely disseminated and pathologically they resemble a tuberculous tubercle without caseation.

There may be spontaneous remission and clinical recovery or there may be impairment of function of the involved organs. Sarcoidosis may show a dramatic response to therapy with cortisone.

Robert H. Durham, M.D.

I have always noticed that God is on the side of the heavy battalions.

—Marquis de la Ferte Imbault

Loss or Destruction of the Scalp —

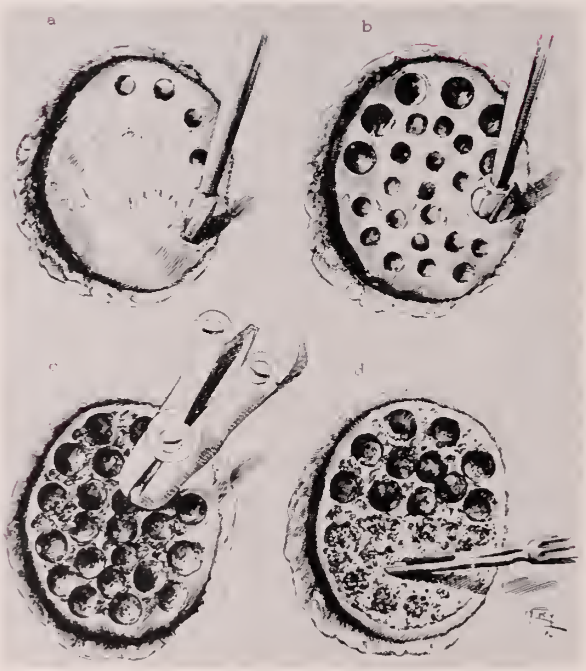

Fig. a, b, c, d. — The procedure employed in removal of the outer table of the skull of patients who have lost a scalp by various burns or incidental to removal of tumors of the scalp. (Reprinted from Western Journal of Surgery 41:65, 1933 with permission of the editors and with permission of the Mayo Clinic Div. of Publications.)

THE HISTORY of the treatment of injuries involving a loss of the scalp is nearly as old as the profession of surgery itself. In recent years, the regrettable custom of scalping ones' enemies has fallen into disuse; and still more recently, industry has put housings and guards around shafts and gears to protect the unwary. However, people continue to sustain thermal injuries, high-speed automobile accidents, and other more bizarre accidents;[1] so that, while rare, scalping still does occur.

Two patients treated recently at the University of Minnesota Hospitals suffered injuries involving the loss of large portions of the scalp including periosteum. The problem, therefore, was one of creating a suitable granulating base for the satisfactory acceptance of split-thickness skin grafts. The purpose of this report is to discuss the management of these patients, to trace briefly the history of the treatment of this type of injury, and to re-emphasize a technique first

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Report of Two Cases and Brief History of the Treatment of this Injury

described by Adson in 1933[2] for the treatment of osteomyelitis of the skull by removing the outer table. We have applied this technique for the purpose of rapidly securing a granulating base.

Case Reports

Case No. 1

This 69-year-old white male was admitted for the first time to the University of Minnesota Hospitals on January 6, 1959. Two days prior to admission, when an oven exploded, he had sustained 25% second and third degree burns over his scalp, face, head, back, and the lateral aspects of both wrists. Entire full-thickness destruction of the scalp was noted from the normal hair line anteriorly to the bregma posteriorly, and from ear to ear.

On the first hospital day, a tracheotomy was performed which resulted in improved management of secretions and respiratory exchange. Initial treatment included parenteral fluids, antibiotics, and sedation. He was able to begin oral alimentation shortly after admission; high-calorie, high-protein meals were instituted. He was remarkably co-operative with respect to caloric intake, which contributed significantly to the success of his treatment.

On the 14th post-burn day, initial debridement and grafting of the burned surfaces on the neck and back were done. By this time, a firm, dry eschar was present over his scalp, measuring 15 by 15 cm. On the 28th day, grafting to his back and wrists was complete. On the 33rd day, the eschar was removed from the skull. An area approximately 3-4 cm. wide around this zone, which had not involved injury to the periosteum, had formed a clean granulating base, leaving an exposed area of bone denuded of all covering and measuring approximately 10 by 10 cm. With a McKenzie 13 mm. perforating twist drill, 60-75 holes were made through the outer table of the exposed bone to a depth at which bleeding was first noted. This corresponded to a point at which only the outer table had been perforated. These holes were then widened with the use of a Hudson burr. Portions of the intervening outer table bridges were then removed with the use of a neurosurgical bone rongeur. Split-thickness skin grafts were applied to the surrounding marginal granulation tissue and excellent takes were achieved.

Granulation tissue was noted to be coming though the holes nine days later (42nd post-burn day); and on the 49th day, when granulations appeared to be proliferating, split-thickness skin grafting was first undertaken. However, because of the presence of bone spicules within the region, the applied grafts took poorly. The remaining islands of outer table bone were removed; and, by the 74th postburn day, a complete granulating base had formed and split-thickness skin grafts were applied with good results.

Case No. 2

This 23-year-old white male was involved in an auto accident on Christmas Day, 1963, in which he was thrown from his car, landing several yards away. He sustained an avulsion of considerable scalp tissue from his left lateral skull, with avulsion of periosteum and actual scoring of the skull by gravel. He lost all of the tissue and tendons from the dorsum of his left hand, and sustained full-thickness abrasion of the skin of his left posterior shoulder. The patient's condition, however, was stable and he was taken to the operating room immediately, where initial debridement of his scalp and hand injuries was performed. Dirt and grease were removed; but debridement of the scalp injury was purposely conservative in order to preserve as much viable periosteum as possible. An area of exposed bone remained measuring 15 by 9 cm.

On the 4th day following admission, further debridement of both wounds was carried out; on the 9th day a full-thickness flap was elevated from the abdominal wall and placed over the defect in the dorsum of the left hand. Continued debridement of tissue surrounding the scalp defect was performed as a granulating base slowly developed. On the 20th day, the patient was taken to the operating room. Under general anesthesia, again utilizing a McKenzie perforating drill, multiple holes were made through the outer table and then enlarged with a Hudson burr. The small bony spicules between these perforations were then removed with a neurosurgical bone rongeur. The remaining bony spicules were removed on the ward over the next three to four days, so that within one week a continuous granulating base was beginning to form and the entire exposed outer table had been removed. Simple sterile vaseline gauze dressings were used, along with systemic antibiotics. By the 30th day, satisfactory granulations covered the entire wound, and two days later, split-thickness skin grafts were taken from the left thigh and placed on the scalp, and a 100% take was achieved. The abdominal flap to the hand wound, which had taken very well, was divided at its base and the abdominal wound closed by approximation of its edges. The patient was discharged on the 45th day.

Follow-up examination five months later revealed the scalp to be very well healed with no sign of ulceration. The patient has been readmitted on two occasions since discharge for tendon grafts to the left hand.

Historical Review of Treatment

Herodotus[3] made the earliest reference to scalping in approximately 450 B.C. when he wrote: "A Scythian drinks some of the blood of the first man he kills, and he brings to the King the heads of all whom he slays in battle. They scalp the heads in this way. . . ." and continued with a detailed description.

Methods for the removal of demarcated, dead skull were described by Celsus[4] as a part of his general description of the treatment of caries of bone. If a small area was to be excised, Celsus recommended the use of a "modiolus," a cylindrical tube with serrated edges to remove a button of bone. For larger areas, trepans were used which were quite similar to our own perforating bits. Rather than boring discrete holes, Heliodorus[5] and Galen preferred to rasp the surface of the skull. None of these practitioners, however, commenced any treatment until demarcation, necrosis, and, no doubt, significant osteomyelitis had developed.

Diploe the Source of Granulation

An excellent and famous monograph on wounds of the head is attributed to Hippocrates,[6] in which methods of healing of exposed skull were described. In speaking of widely comminuted depressed fractures, he noted: "Now the fragments [bone] come up when the flesh grows from below, and it [granulation] grows up from the diploe of the skull and its healthy part if there is necrosis of the upper table of the skull only." Observation and treatment of head wounds allowed Hippocrates to recognize a basic fact: that the diploe was the source of the granulation tissue and that the necrotic outer table had to be absent in order to allow suitable healing.

Advocate Early Trepanning

Augustin Belloste[7] in 1714, in his text on the treatment of many varieties of wounds, noted wounds with exposed skull: "If the bone be uncovered for a considerable extent, with loss of substance, the wound cannot heal for a long time because of its size; and one is not able to prevent the bone from becoming altered and carious by whatever precautions that might be taken. *Now in order to avoid this accident, it is necessary at the first dressing or as soon as possible, to pierce the bone in several places with the pyramid or perforator of the trepan;* in this manner one gives passage to a marrow juice which, oozing out, covers the bone in a short time without loss of the least part of its bony substance." He was thus the first to advocate an early piercing and partial removal of the outer table of the exposed portion of the skull and decried the method prevalent at that time of waiting until the bone became necrotic, demarcated, and often able to be pulled off, a process to which he referred as exfoliation. His reason for early treatment, however, was in error; for he felt that the advantage of piercing the bone was to allow the marrow juice to exude from the diploe and flow over the remaining bone. He failed to recognize that the entire exposed outer table no longer had an adequate blood supply to remain viable.

Early Removal of Bone

Tenon[8] in 1758 was attracted by Belloste's proposals. He presented three papers to the French Academy of Sciences in 1758, 1759, and 1760 on studies of exfoliation of the skull after experimentally-created scalp wounds. He took issue with Belloste's pleas to avoid exfoliation and felt that the healing agent was not a "suc molleux" or marrow juice, but rather the parenchyma of the bone itself, which, as it healed, gave rise to new bone.

Herman Boerhaave,[9] author of a collection of aphorisms and lectures which was widely used as a text in the eighteenth century, cited Belloste's contributions. His aphorism number 249 describes the course of wounds causing pericranial or periosteal destruction and the resultant exfoliation and decay of bone. He correctly laid the cause of this to interruption of blood vessels in the periosteum. Later in his aphorism number 252 he states: "The cure is performed by one gently perforating the bone with a small terebra down to its middle or diploe in several distinct but nearly adjacent places from whence the periosteum will grow up again and prevent an exfoliation of the bone." Again, the idea of avoiding exfoliation and stressing early bone removal becomes paramount. Boerhaave notes, as did Belloste, that untreated wounds usually require 40 days to exfoliate, and made a strong plea similar to that of Belloste for expeditious treatment to avoid intercurrent complications.

In the same year, 1806, as the final publication of Tenon's memoirs, Felix Robertson[10] recorded the experiences of his father, Dr. James Robertson: "In the year 1777 there was a Dr. Vance about the long islands of Holsten (located in the Tennessee River) who was there attending the various garrisons which were embodied in the frontiers of that region to guard the inhabitants against depredations of the Cheerake Indians. In March of the same year, Frederick Calvit was badly wounded and nearly the whole of his head skinned. Dr. Vance was sent for and stayed several days with him. The skull bone was quite naked and began to turn black in places and as Dr. Vance was about to leave Calvit, he directed me, since I was stationed in the same fort with him, to bore his skull as it became blackened and then bored a few holes himself to show the manner of doing it. The time to quit boring is when a reddish fluid appears in the point of the awl, he added. I bored at first about one inch apart, and, as the flesh appeared to rise in these holes, I bored a number more between the first. . . .

"I never knew one that was scalped and bored as above described that did not perfectly recover. There is, however, always part of the scalp over which but little or no hair afterwards grows."

Strayer[11] attempted to trace the origin of this method and to follow its transmission to this country. English and American texts of the 19th century did not mention this procedure, and the French texts of that time minimized the fear of earlier writers over exfoliation. Strayer did conclude, however, that the method of perforation was transmitted to this country by this Dr. Vance, a Scot, who was a travelling surgeon, educated partially at Edinburgh and probably quite familiar with Boerhaave's *Aphorisms.*

Early Removal of Outer Table

No modification in the treatment of scalp avulsions was made until 1933, when Adson,[2] writing on osteomyelitis of the skull, presented a method of total primary removal of the outer table by drilling multiple holes and interconnecting them with a rongeur (Figure 1). In 1946 Kazanjian,[12] dissatisfied with the slow proliferation and coalescence of granulation that occurred with discrete holes, introduced a method of chiseling the surface of the skull with a hammer and chisel until many tiny bleeding points appeared. He reported that from each of these points proliferations arose which ultimately produced an even layer of granulation tissue. Chiseling itself, however, introduces an element of repeated trauma to the head that is undesirable. Another modification was introduced in 1951 by Harrison,[13] who advocated division of the denuded outer table into squares with a circular saw and then removal of the squares with a chisel. The inner table, he notes, is often softened by the pathologic process; and the threat of accidental perforation of the inner table by the chisel is always present.

Historically then, the realization of the processes by which destroyed outer table of skull are healed is ancient. We have progressed over many centuries to appreciate the need for rapid total primary removal of compromised bone. Subsequent to this process, healing cannot be further expedited until grafts are applied and proceeds in their absence exactly as described by Hippocrates.

Discussion

Scalping accidents result in the loss of cranial covering. Exposure of devascularized bone to infection then follows. Subsequent scars and contractures from these injuries can cause severe disfigurement and even optical bulbar injury from loss of lid protection. Aims of treatment are to secure, as soon as possible, an adequate protective covering for the head, minimal contracture of scar tissue, protection of the eyes from secondary injury, and adequate cosmetic repair. These are all largely accomplished now by the use of autogenous skin grafts. Attention must then be given to the most rapid means of preparing a suitable base for skin grafting. Periosteum is itself an adequate base to receive split-thickness skin grafts, because granulation will proliferate from it. When it is lost, desiccated bone will not take grafts and will ultimately become necrotic. When the periosteum is lost, therefore, treatment should be directed in three successive stages: (1) early, total removal of the compromised bone; (2) preparation of a suitable base to allow grafting; (3) rapid covering with split-thickness skin grafts. The bone should be excised as soon as the limits of the injury are definite — usually within one week. Grafting should be done as soon as granulations are complete — in three to four weeks. The experience gained from the two cases presented here shows that the method described by Adson is a simple and safe means to remove only the outer table of the skull. Our experience with the first case taught us a lesson learned by Belloste over 200 years ago. It is essential to remove the entire exposed outer table in order to achieve rapid and complete healing. We were able further to expedite the healing of the scalp wounds in these cases with the use of skin grafting after the granulating base had formed. Robertson mentions that once the necrotic bone had been removed, these wounds often took upwards of two years to heal completely with scar tissue.

More recently, Curtin[16] (1963) has advocated the use of full-thickness pedicle flaps to cover large scalp defects, claiming that the long-term results of split-thickness skin grafting is rather poor. He describes a frequent instance of ulceration, cellulitis, osteomyelitis, and progressive breakdown of skin grafts in his series of patients. We have not as yet noted any of these complications in the two patients which have been reported: one with a five-year repair and one with a six-month repair.

Summary

1. Loss or destruction of significant areas of scalp, while rare, still does occur.

2. Two cases of scalp loss are described, one the result of a severe thermal injury, and the other the result of trauma associated with an automobile accident.

3. The history of the treatment of scalp destruction is traced, noting in particular the trend from allowing a slow exfoliation of demarcated necrotic bone to the recognition for the need of early and rapid removal of the outer table before unnecessary complications and unnecessary wasting of time occur.

4. A method first described by Adson in 1933 for the treatment of osteomyelitis of the skull, which was applied in two cases for purposes of removal of exposed skull, is noted and re-emphasized because it allows rapid, safe removal of the compromised bone.

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PATRON SAINT FOR DECEMBER

Frances Xavier Cabrini

Frances Xavier Cabrini (1850-1917) was an invincible woman of astounding achievements in various fields: particularly in the founding and administration of orphanages and hospitals. A native of Italy, she came to the United States to work among the many recently-arrived Italian immigrants, many of whom were underprivileged, disillusioned, and victimized by exploitation.

Frances' resourcefulness, energy, and persistence were boundless. Starting in New York with contributions totaling $250 she rented a house on East Twelfth Street and furnished it with secondhand beds for which she made the mattresses herself. Inexpensive food from the nearby restaurant warmed up on the hospital's one central stove furnished sustenance for both patients and personnel. A writing desk, a few surgical instruments, and his own services in addition were contributed by a doctor. Thus the Columbus Hospital began functioning in 1892 under the clever and canny management of Frances.

From New York she proceeded to Chicago where, against stupendous odds — major sabotage and strategems to defraud and swindle her — she founded a second Columbus Hospital in the old North Shore Hotel, she herself sharply scrutinizing all financial transactions and supervising even the smallest details of the remodeling. As medical head the hospital was fortunate in securing the famous surgeon, Dr. John B. Murphy.

Frances' two Columbus Hospitals represent only a small fraction of her life achievements but serve to point up her amazing capacity and efficiency.

Only shortly after her death organized pressure began for recognition of Frances' contributions. She was beatified in 1938 and canonized in 1946.

She is the first American saint.

Her day is December 22.

A man gazing on the stars is proverbially at the mercy of the puddles on the road.
—Alexander Smith

IT'S THE LAW

Good Samaritan Statutes

There are eight states which have enacted a Good Samaritan law designed to protect physicians who render emergency care at the site of an accident. These are California, Maine, Nebraska, Oklahoma, South Dakota, Texas, Utah, and Wyoming.

This law states in effect . . . "No person . . . who in good faith renders emergency care at the scene of the emergency shall be liable for any civil damages as a result of acts or omissions by such person in rendering the emergency care."*

Serious questions have been raised as to the future of these laws in the belief that they may be held unconstitutional, and that they may apply only to physicians and could therefore be construed to be class legislation and thus in violation of the special privileges and immunities provision of many of the state constitutions.

Though a physician has an ethical duty to render emergency care, he is under no legal obligation to render such care to persons who are not his patients. Once having volunteered, however, he is required to use reasonable care under the circumstances, and also the degree of skill and care ordinarily exercised by other physicians under the same or similar circumstances.

A Good Samaritan statute has not yet been tested in the courts.

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*West's Ann. Calif. Code, Business and Professions 2144 (Supp. 1961)

ANSWER TO WHAT'S YOUR DIAGNOSIS

(From page 1456)

The man was a worker in the quicksilver mines in Idria near Trieste at the turn of the century and had suffered mercury vapor poisoning, as had many others in the neighborhood.

—G. Durant Hood, M.D., Practical Family Physician, Hood Medical Book Company, 1901

Epilepsy

The nation's two million epilepsy victims have better work-safety records than almost any other group. The Epilepsy Foundation fights for greater employment opportunities for persons with epilepsy. Write to: The Epilepsy Foundation, Washington, D. C., 20005.

Youth is born to be disillusioned and when the process is over, youth is also over.
—Arthur Waugh

Hemangioma

# of the Placenta

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Report of Case

Descriptions of benign vascular tumors of the placenta have appeared periodically in the literature of this country since Ries'[1] report in 1904. The relative rarity and great variability in the appearance of these tumors undoubtedly accounts for the wide range of terminology under which they have been reported, including angioma, fibroangioma, angioblastoma, and chorioangioma. The tendency, in more recent years, has been to include all of them under the term "hemangioma."

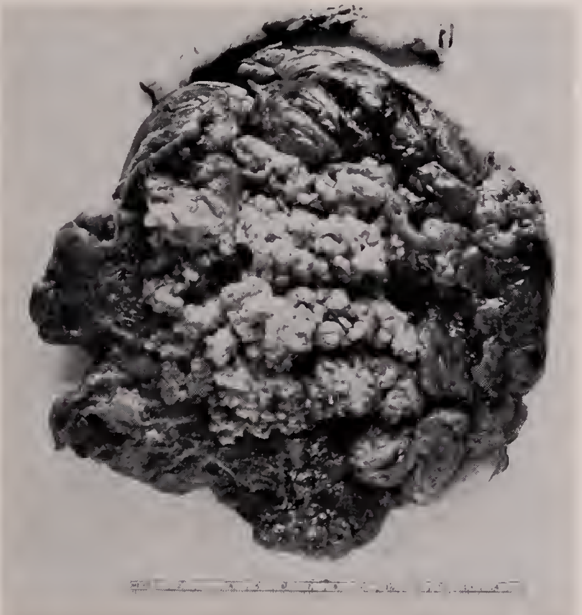

Fig. 1 — Hemangioma of the placenta demonstrating the papillary and nodular excrescences of the tumor on the maternal surface.

The gross appearance of a hemangioma of the placenta is typically described as a single, deep red to brown, circumscribed tumor smaller than a hen's egg and located beneath the amnion on the fetal surface of the placenta. However, multiple hemangiomas may be found, and the lesion or lesions may approach the placenta in size, may be only on the maternal surface or deep within the substance of the placenta, or may be attached to the placenta or cord by a vascular stalk.

The reports of their incidence show a similar variability, for finding them depends largely on the care with which the placenta is inspected. Siddall[2] and Dunn[3] reported an incidence of approximately one per 100 deliveries when placentas are routinely sectioned and examined microscopically. Eastman and Hellman[4] reported an incidence of one per 3500 after careful gross inspection.

Marchetti[5] classified these tumors on a

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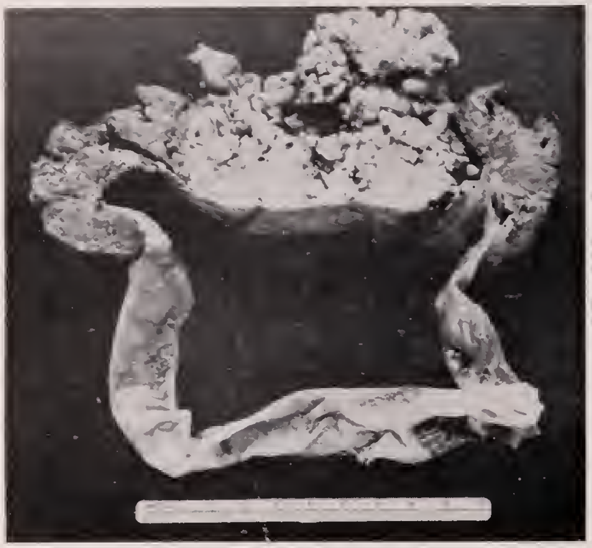

Fig. 2 — The cut surface demonstrating the circumscribed nature of the lesion in the midportion of the placenta and the pale nodular arrangement of the enlarged villi.

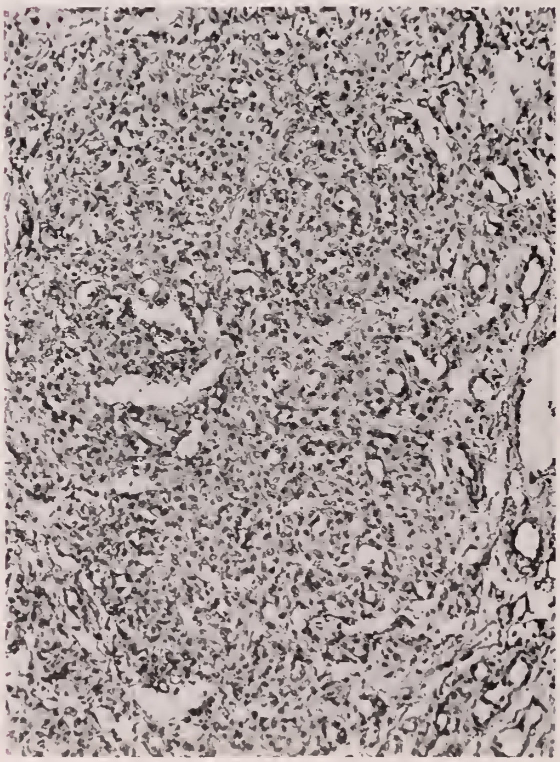

Fig. 3 — The stroma of the placental villi are replaced by closely packed, well-formed, vascular spaces that are lined by plump endothelial cells (hematoxylin and eosin; x100).

microscopic basis into mature, immature, and degenerative types. Most reports describe the mature, or vascular type; but often all three cellular types are seen in the same tumor.

The clinical significance of these tumors has been largely limited to the relatively frequent coexistence of hydramnios and premature labor. Siddall,[6] who reviewed 109 cases of hemangioma of the placenta in 1924, noted excessive amniotic fluid in 40 and premature labor in 35 cases. In a more recent review of 32 cases DeCosta and associates[7] reported premature labor in 12 and hydramnios in nine. They also noted that in three cases the infant had a large associated hemangioma.

The present case, involving a hemangioma of the placenta, is reported because of the rarity of the tumor itself and also to reemphasize the importance of the routine inspection of the placenta following all deliveries.

Report of Case

A 29-year-old white woman, gravida 2, para 1, was admitted at 40 weeks' gestation on August 27, 1963. The course of the pregnancy had been uncomplicated. Her obstetrical history consisted of a normal, spontaneous delivery of a healthy female infant at term in 1960.

The patient was not considered to be in labor. An amniotomy was performed, followed by two 1.0-cc. doses of sparteine (Tocosamine). Onset of labor followed the second dose, and the total duration of labor was 221 minutes.

Delivery of a normal male infant weighing 2870 gm. was accomplished with outlet forceps under pudendal block and nitrous oxide anesthesia. The delivery was followed by moderate bleeding and, for this reason, the placenta was extracted manually and separated without difficulty.

Pathologic Findings

The gross specimen consisted of an enlarged, intact placenta with attached umbilical cord and fetal membranes. The greatest measurements of the placenta in three dimensional planes were 24 by 19 by 5 cm. The fetal-placental ratio was 3.87:1. On the maternal surface the placenta exhibited a somewhat friable, pink-white mass whose surface presented nodular and papillary excrescences. The mass was rather sharply circumscribed in the central portion of the placenta and measured 11 by 10 by 5 cm. (Fig. 1). The cut surface of the placenta revealed that the mass extended to the chorionic plate over a broad surface (Fig. 2). The nodular configuration of the tumor was more apparent on its cut surface than when intact. The nodules accounted for the bulk of the tumor, and, although they were moderately firm within themselves, they tended to separate, giving the tumor the appearance of being friable.

Microscopic Findings

Microscopic examination revealed that the papillary and nodular components were enormously enlarged placental villi, whose bulk for the most part was made up of well-formed vascular channels situated within a delicate fibrous stroma. The capillarylike vascular channels were lined with plump endothelial cells. In focal areas appreciable amounts of fibrous stroma were interspaced between the vascular spaces (Fig. 3).

The surface of the gigantesque villi were lined in part by knots and sheets of syncytial trophoblasts. On the fetal surface of the tumor, islands of the decidual plate were seen (Fig. 4).

In the more cellular areas of the tumor the endothelial cells appeared as cords or masses of cells without a lumen (Fig. 5). Mitotic figures were occasionally observed in these areas. Occasional nucleated erythrocytes were noted in the blood-filled vessels of the tumor, but no foci of hematopoiesis were observed.

Small areas of calcification were seen in the larger fibrous septa within the tumor. The extratumoral placenta exhibited a picture that was consistent with the placenta usually associated with a normal full-term infant.

Summary

In the case reported, a large hemangioma involved the placenta but did not have any apparent clinical effect on the pregnancy, the delivery, or the infant. The importance of routine, thorough inspection of the placenta following each delivery is re-emphasized.

Examination of the mother six weeks post partum showed normal uterine involution.

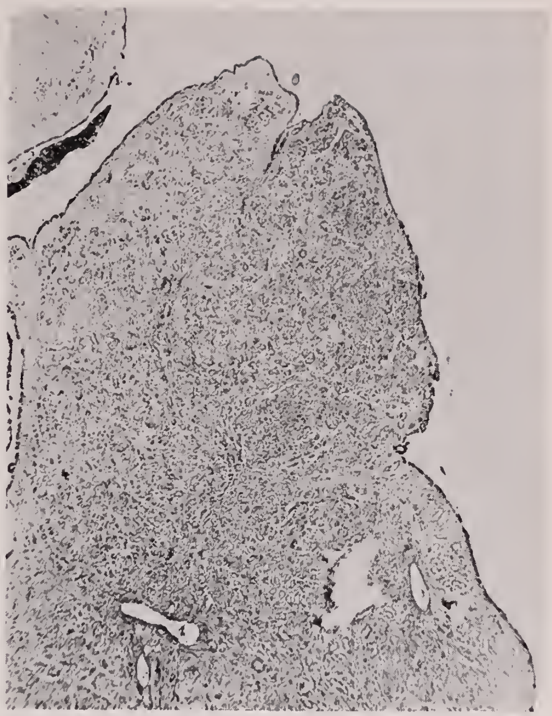

Fig. 4 — Low-power view demonstrating the grotesque distortion of the villi by the hemangioma which accounted for the bizarre gross appearance of the tumor (hematoxylin and eosin; x30).

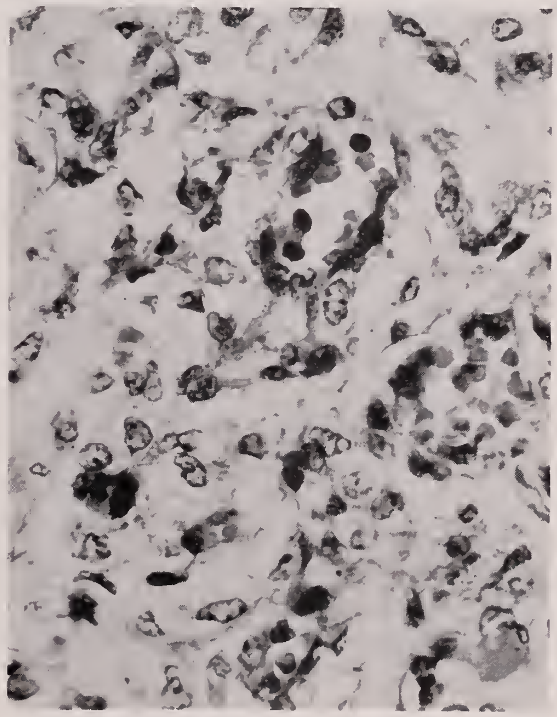

Fig. 5 — High-power view of one of the more cellular areas demonstrating the nature of the plump endothelial cells (hematoxylin and eosin; x600).

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John Arderne to His Colleagues in Surgery

He that would succeed in this art should always set God before him in all his doings, and with heart and soul call for His help. . . . Let him learn to be content in strange places with the meat and drink to be found there, using measure in everything. He should scorn no one. If another doctor is spoken of, he should neither decry him nor praise him unduly, but he may courteously answer, "I have not much knowledge of him, but I have neither learned nor heard anything of him but what was good and honourable."

He must be chaste in word and deed, and he should be guarded in handling and gazing on the wives and daughters or other fair women in great men's houses, lest he cause anger in their relatives. He should avoid giving annoyance to servants. To patients who come to him he should neither be too familiar nor too ungracious. He should not be too ready to undertake every case which offers, and always see it before doing so, and fix his fees, which should not be unduly low. Patients should not be led to expect a cure before a reasonable time. If they do get well very early, you can tell them that it is their good constitution, for they are very delighted to hear that. Let him learn, too, how to comfort his patients with wise reflections, and, indeed, merry tales. He must never disclose the confidences of his patients, whether men or women, nor, indeed, speak ill of anyone, even if he has reason to do so. If a patient sees that he keeps other people's secrets, he will naturally put more confidence in him. John Arderne (1307-1380)

Parker, G., M.A., M.D., M.R.C.S.: Early History of Surgery in Great Britain. A. & C. Black LTD., London 1920.

Hippocrates on Prognostics

It is in my opinion a most excellent thing for the physician to practice forecasting. For, by discovering and announcing independently, in front of his patients, their present condition, the events that have led up to it, and those that are going to follow, also by pointing out what the patient has omitted to state, he (the physician) will gain an enhanced reputation for understanding illness, and so men will be ready to entrust themselves to him. Treatment also will be best carried out by him if he already knows what course the existing malady is going to take.

Blessed is the man who is too busy to worry in the daytime, and too sleepy at night.—Church Management

The Doctor's Visit, Jan Steen 1626-1679, Mauritshuis, The Hague

In Diverticulosis and Diverticulitis…

METAMUCIL® brand of psyllium hydrophilic mucilloid

"**Diverticulosis** … a low-roughage diet is advisable.… Constipation is avoided, preferably by the daily use of Metamucil.

"**Diverticulitis** Mild, chronic symptoms of diverticulitis, such as diarrhea or flatulence also are treated[1] by low-roughage diet, adequate fluid intake and Metamucil.…"

Usual Adult Dosage: One rounded teaspoonful of Metamucil (or one packet of Instant Mix Metamucil) in a glass of cool liquid one to three times daily.

Metamucil is available as Metamucil powder in containers of 4, 8 and 16 ounces and as flavored Instant Mix Metamucil in cartons containing 16 and 30 single-dose packets.

1. Welch, C. E., Diverticula of the Alimentary Tract, in Conn, H. (editor): Current Therapy—1961, Philadelphia, W. B. Saunders Company, 1961, pp. 224-225.

SEARLE

Research in the Service of Medicine

The discharged mental patient . . . and Thorazine®

brand of chlorpromazine

"The average practitioner is quite capable of handling the vast majority of ex-institutionalized patients by regulation of medication, reassurance, manipulation of the environment where necessary, and . . . other technics." Kline, N.S.: Postgrad. Med. 27:620 (May) 1960.

The family physician must often assume responsibility for the discharged mental patient. Thorazine (chlorpromazine, SK&F) can be a valuable adjunct to the continuing care of this patient, because it helps prevent relapses by insulating him from the impact of stressful experiences. For successful rehabilitation and prevention of rehospitalization, however, the former mental patient—and often his family—also needs the guidance and counsel of his physician.

Many physicians are surprised by the high doses of Thorazine (chlorpromazine, SK&F) used in patients released to their care from mental hospitals. This surprise may be expressed by a drastic reduction in dosage "to play it safe"—with serious consequences for the patient.

The successful maintenance of former mental patients requires adequate, often "high" dosage, and often for prolonged periods of time. Fortunately, these dosages do not mean greater risks for the patient. On the contrary, there is much less risk of serious side effects once a patient has become gradually accustomed to Thorazine (chlorpromazine, SK&F)—*regardless of dosage*—over a period of a few months. Continuing therapy is almost always well tolerated, and is essential to most patients' continued well-being.

Brief Summary: Thorazine (chlorpromazine, SK&F) has been successfully used for 10 years in the treatment of mental and emotional disturbances, and has proven highly effective in the maintenance therapy of former hospitalized mental patients. *Principal side effects:* The most frequently encountered side effect is transitory drowsiness. Other occasional side effects include: dry mouth, nasal congestion, constipation, miosis, dermatological reactions, photosensitivity, jaundice, hypotension, increased appetite and weight; very rarely, mydriasis, agranulocytosis, extrapyramidal symptoms. *Contraindications:* Comatose states or in the presence of excessive amounts of C.N.S. depressants.

For complete prescribing information, please see *PDR* or available literature.

SK&F *Smith Kline & French Laboratories*

Editorials

Direct-Current Shock in the Treatment of Cardiac Arrhythmias

THE ELECTIVE use of direct-current shock in the treatment of cardiac arrhythmias was introduced by Lown and associates[1] in 1962. Because of the safety and effectiveness of this technic, it has been widely applied clinically and has profoundly altered the treatment of arrhythmias. Accurate placement of the electrical discharge during the cardiac cycle reduces the risk of ventricular fibrillation.

In the series reported by Hunter and Richards[2] approximately 90 per cent of the arrhythmias treated by direct-current shock were successfully converted to sinus rhythm, and this degree of success is in keeping with the large series reported by Lown and associates.[3] Atrial flutter has continued to be the most susceptible disturbance. The technic has proved effective in the treatment of drug-resistant cardiac arrhythmias as reported by McDonald and associates.[4] The shock is probably best administered after the patient has been placed under light general anesthesia in order to avoid the unpleasant subjective sensations that accompany the shock.

Anticoagulant coverage should be administered to all patients who have a substantial risk of embolism. Use of digitalis should be discontinued well before the shock is administered, and treatment of patients with frequent ventricular extrasystoles should be avoided.

The choice of patients for conversion of chronic atrial fibrillation to sinus rhythm remains the major problem. The primary reason is the frequent relapse to atrial fibrillation, and if the rhythm is unstable, well-controlled atrial fibrillation is preferable to frequent changes of rhythm.

In conclusion, a safe and effective technic has been developed for the treatment of cardiac arrhythmias. It is important that the use of this technic be carefully considered in its clinical application to each individual patient.

Robert J. Schultz, M.D.
Emilio R. Giuliani, M.D.
Rochester, Minnesota

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1. Lown, Bernard, Amarasingham, Raghavan, Newman, Jose, and Berkovitz, Barouh: The Use of Synchronized Direct-Current Countershock in the Treatment of Cardiac Arrhythmias. Read at the Fifty-fourth Annual Meeting of the American Society for Clinical Investigation, Atlantic City, New Jersey, April 30, 1962. J Clin Invest 41:1381, 1962.

Continued

"Wonderful...haven't had opening in both nostrils for years"*

(clearly decongested with Dimetapp)

Dimetapp lets your "stuffed-up" patients *breathe easy again.* Each long-acting Extentab works hard for up to 10-12 hours clearing away stuffiness, turning off the drip, and unplugging congestion that accompanies upper respiratory conditions. Yet, patients seldom experience drowsiness or overstimulation. (A key to success: the Dimetapp formula.) Now that the "stuffy" season is here, keep dependable Dimetapp Extentabs on tap. They get the job done.

FOR NASAL DECONGESTION IN SINUSITIS, COLDS, U.R.I.

UP TO 10-12 HOURS' CLEAR BREATHING ON ONE TABLET

Dimetapp® Extentabs®

(Dimetane® [brompheniramine maleate], 12 mg.; Phenylephrine HCl, 15 mg.; Phenylpropanolamine HCl, 15 mg.)

BRIEF SUMMARY: Indications: Dimetapp reduces nasal secretions, congestion, and postnasal drip for symptomatic relief of colds, U.R.I., sinusitis, and rhinitis. **Side Effects:** In high dosages, occasional drowsiness due to the antihistamine or CNS stimulation due to the sympathomimetics may be observed. **Precautions:** Administer with caution in the presence of cardiac or peripheral vascular diseases and hypertension. **Contraindications:** Antihistamine sensitivity. Not recommended for use during pregnancy.

*Clinical report on file, Medical Department, A. H. Robins Co., Inc.

A. H. ROBINS CO., INC., RICHMOND 20, VA.

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4. McDonald, Lawson, Resnekov, Leon, and O'Brien, Kevin: Direct-Current Shock in Treatment of Drug-Resistant Cardiac Arrhythmias. Brit Med J 1:1468, 1964.

Pyloric Stenosis

As DR. LOWELL W. BARR* has pointed out, both jaundice and hematemesis may be associated with pyloric stenosis. The hematemesis or melena has usually been dismissed as a result of the trauma of vomiting and gastric distention. The cause of the jaundice has been more difficult to establish.

As a result of experience with several patients who have had a combination of pyloric stenosis and jaundice, I have come to the conclusion that there is more than one cause and sequence of events, although their association seems to be beyond the limits of pure chance. In my own experience, the association of jaundice and pyloric stenosis has been almost 100 per cent in female children, and this peculiarity suggests in some vague way the incidence of choledochal cysts in females.

Having become enthusiastic about the possibility that the pyloric tumor could create obstruction to the common bile duct through compression due to tightness of the gastrohepatic ligament and peritoneal folds, I decided to demonstrate this with a motion picture of the operation in the next patient who came under my care. This motion picture is now available through the American College of Surgeons Film Library. There were several interesting points made in this film. First of all, jaundice began one week after birth. The patient presented for treatment at five weeks of age, and at this time the total bilirubin was 13.5 mg. %, of which 9.4 mg. % was direct and 4.1 was indirect. At operation, the pyloric tumor was easily delivered into the wound and appeared to be on a relatively long apron; in no way did it show any possible compression or kinking of the common bile duct, cystic duct, or gallbladder. Simple pyloromyotomy resulted in almost immediate diminution of the jaundice. A liver biopsy taken at operation revealed a normal liver without evidence of bile stasis. Ten days later the total serum bilirubin was 5.9 mg. % ; the direct was 4.2 mg. %, and the indirect 1.7 mg. %. A month later, the values were completely normal.

Certainly this is tangible evidence of at least one case in which the compression theory is not satisfactory in spite of the fact that the direct bilirubin had led us to anticipate true obstructive jaundice. The variations in all aspects of the cases that I have since seen suggest multiple processes that are fascinating from the academic standpoint but which have little influence on the outcome of the cases.

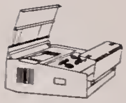
Hugh B. Lynn, M.D.
Rochester, Minnesota

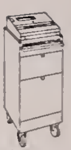
References

1. Barr, Lowell W.: Pyloric Stenosis with Hematemesis and Jaundice. Minnesota Med 47:934, August.

Progress Note

Economy — A very forthright Swedish lady in paying her bill said "I yust wish I had seen doctor $40.00 earlier."





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Model 500 Viso-Cardiette, $695 complete (delivered, continental U.S.); with optional Model 500-1100 Cart, $820. Call your local Sanborn Branch Office now. Sanborn Company, Medical Division, Waltham, Mass. (02154), a Division of Hewlett-Packard.

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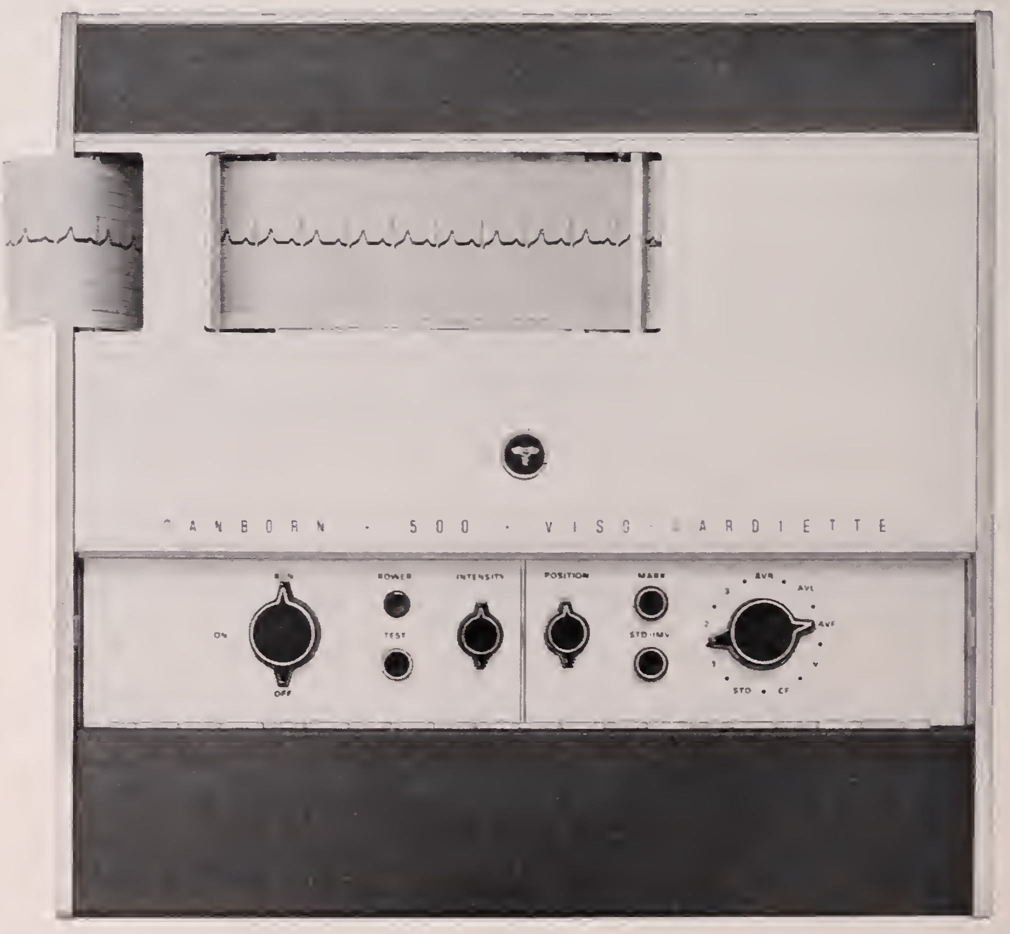

Neoplastic Diseases in the Metropolitan Twin City Area

DR. ROBERT HEBBEL* has brought up to date the monumental study started by Dr. Bell tabulating neoplastic deaths from the autopsy protocols of the University of Minnesota Department of Pathology. Periodic progress reports of this continuing study should stimulate further efforts to use this vast reservoir, far in excess of 100,000 cases, to map out behavior patterns of other diseases.

Of special interest is the six-fold increase of lung cancer deaths in Minnesota during the course of the study. This sobering statistic again brings close to home the alarming increase of lung cancer deaths which now head the list of fatal neoplasms in males. For the last period tabulated (1958-1962) this cancer, which may be preventable, caused one in every fifteen cancer deaths.

A more hopeful but still unexplained and intriguing occurrence over the past decade has been the very real decrease in incidence of cancer of the stomach. Whereas a generation ago, this was the most common cause of cancer death in males in the western world, it no longer occupies this primary position. Some have been reluctant to accept the apparent decrease in incidence of gastric cancer as real, but these figures of Dr. Hebbel further confirm and substantiate an observed national trend. The use of this vast collected pathological data for studies such as these, which in summation give the substance of fact to an apparent trend, will in time stimulate further thought and study so that the cause of this occurrence will become known. At the moment however, an acceptable and proven explanation of this phenomenon has not been advanced.

Arnold J. Kremen, M.D.
Minneapolis, Minnesota

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*See *Minnesota Med.*, 47:1227, 1964.

Heavy Metal Intoxications

ELSEWHERE IN this issue of Minnesota Medicine* there appears an article concerning several cases of metallic mercury poisoning in one family. Metallic mercury is ordinarily an innocuous substance which can be ingested with no untoward effects. However, the metal does have an appreciable vapor pressure and, if finely divided enough, geometrically increasing its surface area per unit of mass, dangerous air concentrations can result. Significant amounts may also be vaporized if the material is heated.

The cases discussed in this issue, although the mode of exposure is unusual, typify the hazards of the group of elements known as heavy metals. In addition to mercury, arsenic, lead, beryllium, thallium, and cadmium are representatives of this series. Lead and its compounds have been a major industrial hazard in foundries and smelters for many years, and even today illnesses resulting from exposure to lead fumes account for a large part of the occupational disease reports received by the State Board of Health each year. Lead is also a significant hazard to children. Poisonings occur when toddlers eat old paint flaking from woodwork and plaster surfaces dating back to the time when lead was a common paint pigment. Fortunately lead has recently been largely replaced by better and less toxic pigments. The hazard,

Continued

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*See Page 1457.

"Gesundheit!"

...is just for the sneeze

but for symptomatic relief of the common cold...

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TABLETS

Each layered tablet contains:

'Sudafed'® brand Pseudoephedrine Hydrochloride	20 mg.
'Perazil'® brand Chlorcyclizine Hydrochloride	15 mg.
Phenacetin	150 mg.
Aspirin	200 mg.
Caffeine	30 mg.

To relieve the aches, pains, fever and respiratory congestion of the common cold, flu or grippe with one product ...specify 'Emprazil'.

Caution: While pseudoephedrine is virtually without pressor effect in normotensive patients, it should be used with caution in hypertension. Also, while chlorcyclizine has a low incidence of antihistaminic drowsiness, the usual precautions should be observed.

Supplied: Bottles of 100 and 1000.

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however, remains in older buildings, and each year a number of serious poisonings occur from lead eaten by small children in the Twin Cities area alone.

The variety of arsenic-bearing compounds available on the market shelves is remarkable, and arsenic (like strychnine and cyanide) can be purchased quite readily at almost any pharmacy. One well-known and popular ant-control product contains lethal quantities of arsenic, and this product alone accounts for at least 100 childhood poisonings of varying severity each year in the Twin Cities. Another product available in every garden shop and hardware store contains 50% available arsenic, and it is sold in quarts and gallons. A few drops of the product would be a fatal dose for an infant.

Beryllium is an industrial metal which has been in use for only a few years, but the machining and casting of this metal present serious problems in these industries, and elaborate techniques have had to be developed to minimize the dangers from it.

Thallium is an ingredient in several household product types such as hair dyes, and cadmium is both an industrial problem and a home hazard. Recently attention has been called to acute poisonings resulting from the use of cadmium-plated refrigeration shelves as outdoor picnic food grills.

The diagnosis of heavy metal intoxications requires an awareness of the potential danger of these metals in the home and work environment. Where suspicion is raised, a careful history will usually reveal whether or not a significant contact with any of these agents has occurred. Confirmation by chemical analysis of blood and of urine specimens completes the diagnosis.

The Minnesota Department of Health provides laboratory and consultative services for all toxicological diagnostic problems, of which the heavy metals represent only one special group. Each year several thousand specimens ranging from urine and blood to biopsy and autopsy material are analyzed for concentrations of specific toxic elements and compounds. Consultation is available from the Department through both the Central Center of the Minnesota Poison Information Network and the Section of Occupational Health. The accumulated experience of the Department in toxicological problems is often valuable to physicians faced with a diagnostic dilemma of possible toxicological etiology. In addition the Department will undertake investigations of suspected environments, including measurements of air concentrations for a wide variety of dangerous materials.

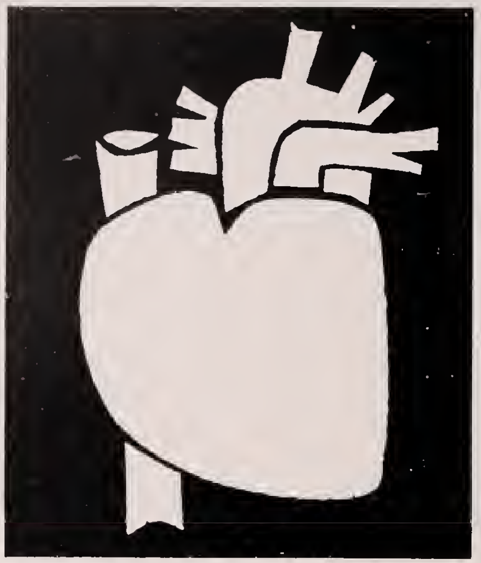
Many of the nonindustrial exposures to the heavy metals occur in circumstances bordering on the bizarre. Most other nonindustrial intoxications result from ignorance about or careless disregard for the toxic nature of products formulated with these metals or their compounds. When presenting symptoms suggest the possibility of metal poisonings, a thorough review of the home and work activities should be made. Based then upon known or suspected contacts with the toxic agents, laboratory studies can provide the physician with an accurate evaluation of the significance of exposure and its relationship to the illness of the patient.

W. R. Lawson, M.D., Chief
Sec. of Radiation & Occupational Health
Minnesota Department of Health

The Editor's Soliloquy

People with psychological or emotional problems often project on to others the symptoms from which they themselves suffer. Beware, lest you inflict suffering in demanding obedience to your conscience. You may be suffering from a case of conscience-itis. We have dissected our bodies to the ultimate, perhaps we should start dissecting our minds. — C.O.R.

A CONSERVATIVE Rx FOR A CLASSIC Dx



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ANTERIOR
VAGUE IN CHARACTER
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SUBSTERNAL

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Effective tranquilization
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long-acting coronary vasodilation
for
prophylaxis of pain in angina pectoris

Indications: 'Miltrate' is useful for prophylaxis of pain in angina pectoris and coronary insufficiency, especially where anxiety is a factor. **Contraindications:** Like all nitrates, pentaerythritol tetranitrate should be avoided or prescribed cautiously for patients with glaucoma. Previous allergic or idiosyncratic reactions to meprobamate contraindicate subsequent use. **Precautions:** *Meprobamate* — Patients engaged in activities requiring alertness should be warned of drowsiness. Meprobamate may increase the effects of excessive alcohol, and the possibility of dependence should be considered, particularly in patients with a history of drug or alcohol addiction. Sudden withdrawal may result in reactions, rarely epileptiform seizures. Grand mal attacks may be precipitated in persons susceptible to both grand and petit mal. Prescribe cautiously and in small quantities to patients with suicidal tendencies. **Side effects:** *Pentaerythritol tetranitrate* — The most common side effects are transient headache, nausea, and rash. Weakness, palpitation, flushing, gastrointestinal distress, and lightheadedness have been reported on a few occasions. *Meprobamate* — May cause drowsiness and, rarely, ataxia, usually controlled by decreasing the dosage. Allergic or idiosyncratic reactions are rare, generally developing after one to four doses of the drug. Mild reactions include urticarial or maculopapular rash. Serious reactions, rarely encountered, include dermatological effects, acute nonthrombocytopenic purpura, chills, fever, fainting spells, angioneurotic edema, bronchial spasm, hypotensive crisis, anuria, anaphylaxis, stomatitis and proctitis. Treatment should be symptomatic, and the drug not be reinstituted. **Dosage:** Usual dosage is one or two tablets before meals and at bedtime. Individualization of dosage is required for maximum therapeutic effect. Doses above twelve tablets daily are not recommended. **Supplied:** White tablets, each containing meprobamate 200 mg. and pentaerythritol tetranitrate 10 mg. *Before prescribing, consult package circular.*

WALLACE LABORATORIES / Cranbury, N. J.

CML-4087

Letter to the Editor:

A book — FAMILIAR MEDICAL QUOTATIONS — which we hope will be a great collection of wit and wisdom from and about physicians of the ages is being assembled. The writings and utterances of physicians, teachers and investigators from the dawn of medical history to the present are being sifted for the nuggets of genius and brilliant good humor which characterize the humanity of a profession. The collection will also include quotes from lay writers — including the Scriptures — dealing with disease, doctors and medical life.

We are particularly anxious to obtain the quotations of individuals who, unlike Shakespeare and Osler, have hidden their occasional gems so that only a few are aware of them.

We welcome all such favorite quotes that your readers would like to see included in this volume. Contributions may be addressed to me c/o FAMILIAR MEDICAL QUOTATIONS, 34 Beacon St., Boston, Mass. 02106.

Maurice B. Strauss, M.D.
Editor

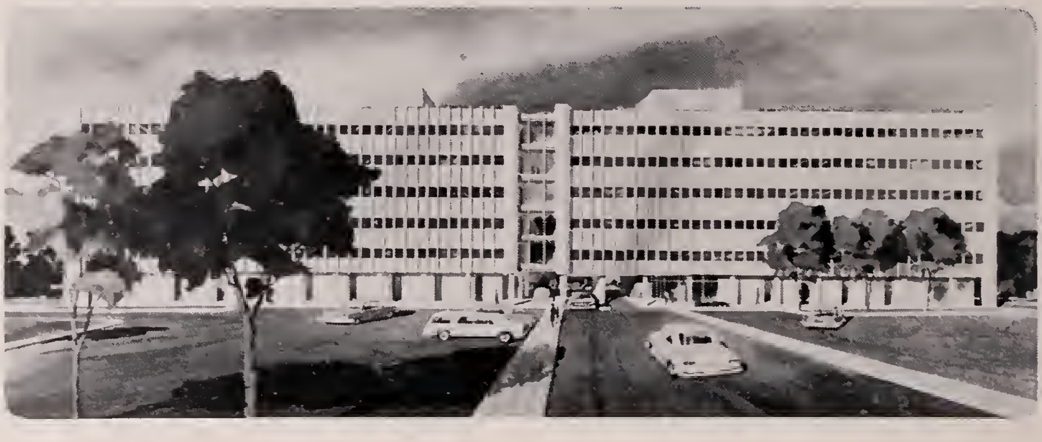
Knee Chest Position

I wonder what the doctors see
When they perform proctoscopy.
What lesson do they hope to learn
From labyrinthian twist and turn —
Or is it that they're in the mood
To test intestinal fortitude?

If so, will someone tell me why
They dare not look me in the eye?
What manly courage do they lack
That they do this behind my back —
This practice one can but define
As positively assinine.

I'll take needles, offer blood,
Give out samples in a flood,
But adamant, I will not cope
With that infernal proctoscope —
That instrument of low degree
That dares invade my privacy.
I will not stoop nor bow nor bend
Proctoscopy! It is the end.—Avner Rakov

Lincoln was right, of course; you can't fool all of the people all of the time; but you only have to fool a majority.



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Curbstone Consultation

Welders and X rays

QUESTION: Several cases have come under my attention in which welders have presented with abnormal chest X rays. These individuals have been involved, so far as I can determine, almost exclusively in the welding of iron products. In most cases they do not have any respiratory symptoms, but the chest X rays in all cases show extensive bilateral clouding. What is the prognosis and treatment of such cases?

ANSWER: It is not uncommon for welders exposed to the fumes and dusts resulting from welding to exhibit marked lung changes by chest X ray. Despite the rather frightening appearance that may be demonstrated roentgenographically, there is no good evidence that the inhalation of iron dusts or fumes results in changes leading to pulmonary disability. It is important, however, to determine the composition of the electrodes used in such work. Electrodes may contain elements that can become incorporated in the fumes during welding, and when inhaled can lead to eventual pulmonary fibrosis and respiratory disability. Preventive measures should be directed towards ensuring adequate ventilation in the work area and to encourage the welders to be properly masked.

Asymptomatic Cholelithiasis

QUESTION: I have a 46-year-old diabetic patient with cholelithiasis. This woman is essentially asymptomatic and, except for diabetes mellitus easily managed by diet and orinase, is otherwise in good general condition. In the nondiabetic I have not considered asymptomatic cholelithiasis as an indication for surgery. Should I apply the same indications to the patient in question with diabetes?

ANSWER: Elective surgery for uncomplicated cholelithiasis (or chronic cholecystitis) carries an operative mortality and morbidity not appreciably different in the diabetic as compared with the nondiabetic patient. Most surgeons, however, find that when emergency surgery is necessitated to deal with the acute complications of cholelithiasis in diabetic patients, the operative mortality will be four to five times greater than in a similar nondiabetic group of patients. The increased mortality and morbidity, to be sure, are found principally among the group of severe diabetics. However, because of a high incidence of later complications developing in even mild diabetics with cholelithiasis, elective cholecystectomy should be performed when the diagnosis is made in the absence of a specific contraindication.

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Fracture–Trauma Conference

Full-Thickness Skin Loss Over A Flexor Tendon

Full-thickness loss of skin and subcutaneous fat presents a particularly pressing problem when it occurs on the volar surface of a finger. If such a wound is not covered immediately by a tissue of similar composition, there is likely to be a marked restriction of tendon motion because of adhesions and scarring, and a disabled finger and hand will be the result. Since free grafts of skin and underlying fat are not likely to "take" over a tendon, it is frequently necessary to utilize a pedicle-type graft. The following case history is of interest.

Case History

An 83-year-old female seamstress was admitted to Swedish Hospital on February 3, 1964. While laundering her clothes the forefinger of her right hand was caught up in the wringer and severely injured. Examination in the Emergency Room revealed a full-thickness loss of soft tissues the size of a dime over the volar aspect of the proximal interphalangeal joint, exposing the flexor profundus tendon. X rays revealed no fractures.

The patient was taken to the operating room and under general anesthesia the entire hand was prepared and the wound copiously irrigated with normal saline. It became obvious that there was too much loss of tissue to allow for primary closure without a graft. Therefore a full thickness flap was outlined and then raised from the adjacent radial aspect of the middle finger. A free split-thickness graft from the thigh was used to cover the donor site, and then the pedicle was swung into the defect of the forefinger and sewn into place with 5-0 nylon sutures.

Plaster-split immobilization was used for one week. At the end of this period the graft appeared quite viable, and observation with the finger in flexion and extension revealed good circulation to even its most distal portion. Therefore the fingers were taped together, and the patient was allowed to use her hand and fingers for limited home duties.

At the end of 29 days under local 1% procaine anesthesia the pedicle was divided. The graft had taken well and when the patient was seen last on June 17, 1964, she had good motion of both forefinger and middle finger and was back at work.

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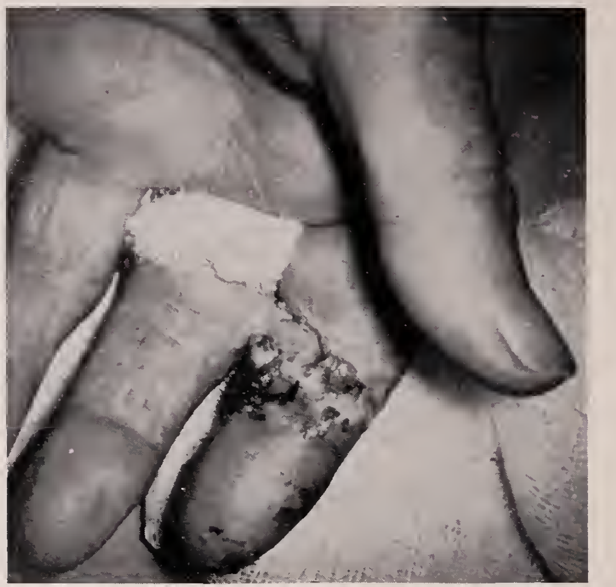

Fig. 1 — Cross Finger Pedicle Graft at 29 days.

Discussion

There are several available donor sites for the pedicle graft in such a case. However, whether the donor site be the thenar eminence, chest wall, abdomen, or thigh, it would require a period of immobilization of from three to five weeks duration in order to insure an adequate new blood supply. In this instance it was necessary to insist upon one week's immobilization to allow for wound healing. This was accomplished with a plaster splint. At the end of this period free flexion and extension were permitted by simply taping the fingers together, thus allowing use of her hand during the remainder of her convalescence and preventing the finger stiffness that might have resulted if another donor site had been chosen.

Bunnell recommends that a Kirschner wire be placed through the phalanges in such a cross finger graft to hold the position.* In this case such fixation seemed undesirable at the time of surgery and would have been unnecessary, as her subsequent course proved.

It is noteworthy that this remarkable octogenarian has returned to her work as a seamstress with essentially no finger disability.

Harrison H. Farley, M.D.
Minneapolis, Minnesota

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*Bunnell's Surgery of the Hand. Boyes, 4th Edition, Pg 194, 1964.

* * *

When a man is born, people say, "How is the mother?" When he marries, they say, "What a beautiful bride!" And when he dies, they say, "How much did he leave her?"—Advertisement of Life Insurance Company of Virginia

* * *

The man who waits for things to turn up finds his toes do it first.

Tumor Conference

Carcinosarcoma of the Esophagus*

Carcinosarcoma of the esophagus is a rare malignant lesion containing both epithelial and mesodermal neoplastic elements. Moore and associates[1] in 1963 found 27 case reports of this tumor in the literature and described a patient of their own who was free of evidence of recurrence five and one-half years after excision of the tumor. We have been able to find only eleven additional case reports of this unusual esophageal tumor,[2-8] including the patient described below:

Case History

A 55-year-old white male was admitted to Ancker Hospital on August 25, 1964, with a five-month history of chest pain, progressive dysphagia and 35 lbs. weight loss. At the time of admission he could swallow only liquids. His past medical history was unremarkable and there were no other symptoms. On physical examination the patient appeared chronically ill and older than his stated age, with signs of obvious weight loss. The breath was extremely foul. Physical examination was not otherwise remarkable. Laboratory findings included a hemoglobin of 13.9 gm., white blood count of 8,700 with a normal differential and essentially normal urinalysis. Serum proteins were total: 7.5 gm. with albumin 3.6 gm., and globulin 3.9 gm. Blood sugar, urea nitrogen, serum bilirubin and alkaline phosphatase were normal. Esophagram demonstrated a large irregular mass protruding into the lumen of the distal third of the esophagus (Figure 1). Upper gastrointestinal X-ray examination was not otherwise remarkable.

Esophagoscopy

Esophagoscopy was carried out on September 1, 1964. There was a considerable amount of retained food particles in the esophagus. A nodular mass protruded into the distal esophagus, and there appeared to be a granular flat projection on the posterior wall of the esophagus at junction of middle and distal thirds. Biopsy of the nodular tumor mass demonstrated a high grade squamous-cell carcinoma invading the underlying stroma, composed of malignant-appearing spindle cells. The diagnoses of carcinosarcoma or pseudosarcoma were considered.

Thoracotomy

Thoracotomy was carried out on September 4, 1964. There was a freely movable mass in the distal esophagus, which appeared to be attached to the wall at about the junction of middle and lower thirds. Frozen section examination of large lymph nodes in the posterior mediastinum, paracardiac area, and along the left gastric artery demonstrated no tumor. The distal two thirds of the esophagus was removed and alimentary continuity re-established by esophagogastric anastomosis. Except for a superficial wound infection the patient made an uneventful recovery.

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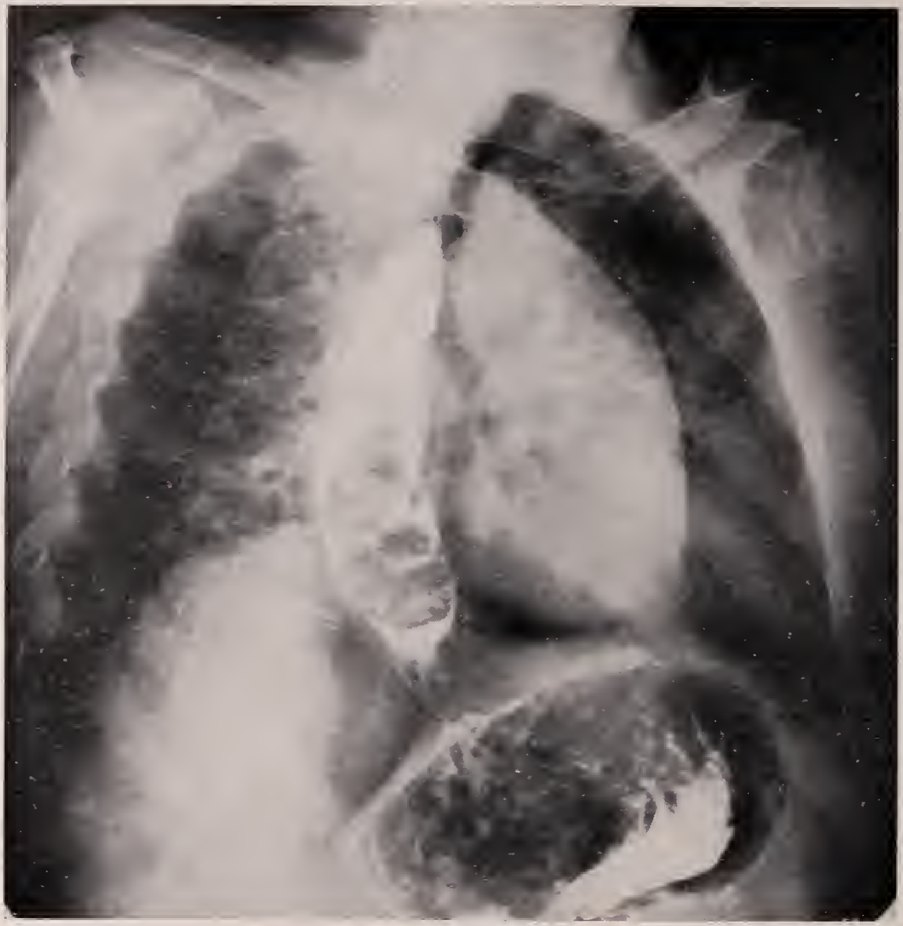

Fig. 1 — Esophogram demonstrating pedunculated tumor mass in the lumen of distal esophagus.

Pathological Examination

Gross Findings

The tumor and 10.0 cm. of distal esophagus were submitted for examination. Near the proximal line of resection, a polypoid tumor measuring 8.0 x 4.0 x 3.5 cm. was attached to the esophageal mucosa by a stalk 0.7 cm. in length (Figure 2). The mass was firm, rubbery in consistency, nodular, yellow-white in color, with small areas of hemorrhage on the surface. The cut surface appeared whorled, reminiscent of a leiomyoma. Small hemorrhages, 1 to 2 mm. in diameter, were scattered throughout the tumor. On the esophageal mucosa were numerous areas of leukoplakia.

Microscopic Findings

Microscopically two distinct malignant elements were present. Squamous-cell carcinoma on the surface of the tumor, with both fairly well differentiated and highly anaplastic areas (Figures 3 & 4), invaded the underlying stroma composed of malignant spindle cells. The cells of the mesodermal elements varied greatly in size, many with large hyperchromatic pleomorphic nuclei. Numerous pathologic mitotic figures and tumor giant cells were present. Many of the spindle cells resembled the racquet cells and strap cells seen in rhabdomyosarcomas, but cross-striations could not be found. Other areas of the tumor were extremely varied in structure, resembling fibrosarcoma, angiosarcoma, leiomyosarcoma, and neurofibrosarcoma (Figures 5 & 6). Ulceration of the epithelial neoplasm was seen in several areas. Small foci of calcification and collections of brown pigment-containing macrophages were also present. The pedicle and surrounding esophageal mucosa were free of tumor but showed changes consistent with leukoplakia. An additional 1.2 cm. of esophagus was resected from the proximal end; this also was free of tumor.

Discussion

Carcinosarcoma

Carcinosarcoma has been described in the lung, thyroid, breast, uterus, and urinary tract, as well as in the esophagus, with the uterus accounting for the majority of the reported cases. The origin of these peculiar tumors is unknown, but the most frequently cited hypotheses are: a) *Collision Tumors,* wherein two malignancies, one of epithelial tissue, the other of mesodermal elements, arise coincidentally at separate points, then grow toward each other; b) *Combination Tumors,* which, according to Meyer,[9] occur when one stem cell gives rise to two blastomatous elements; c) *Composition Tumors,* wherein both elements become malignant, presumably simultaneously, and d) *Sarcomatous Changes* occurring in the previously benign connective tissue of malignant epithelial neoplasm. Saphir and Vass,[10] and Perlman[11] have expressed doubt of the dual nature of these neoplasms and suggest that the histopathological appearance is simply a manifestation of metaplasia occurring in squamous-cell cancer of the esophagus. The problem is further complicated by the well known tendency for spindling, anaplastic squamous-cell carcinomas to mimic sarcomas. *"Pseudosarcoma"* must also be considered.[12] This is a sarcoma-like change in the connective tissue underlying a squamous-cell carcinoma and has been observed in the oral cavity, the base of the tongue, and the larynx. Since the sarcomatous element of this neoplasm has never been known to metastasize, this seems to be a neoplasm distinct from carcinosarcoma.

Esophageal Carcinosarcoma

In most of the reported cases of esophageal carcinosarcomas, the malignant epithelial element has been squamous-cell carcinoma. Talbert and Cantrell[2] describe one case in which well differentiated squamous-cell carcinoma, adenoid-cystic carcinoma, and undifferentiated sarcoma were present. Other types of adenocarcinoma have also been reported in these tumors. The mesodermal neoplasm, in most cases, has been described as undifferentiated sarcoma; but leiomyosarcoma, rhabdomyosarcoma, and fibrosarcoma have also been reported. In the present case, the epithelial tumor has both well differentiated and anaplastic features. The mesodermal elements are distinct and highly malignant. It is felt that both the gross and the microscopic features of this tumor fulfill the criteria for a carcinosarcoma. The sarcoma was varied in microscopic appearance, and if one accepts the definition of a mixed mesodermal tumor as being one in which two sarcomatous elements, other than fibrosarcoma, are found, this tumor can be called a carcino-mixed mesodermal tumor.

As pointed out by Stout and Lattes,[12] carcinosarcoma of the esophagus takes two gross forms: one a pedunculated tumor, usually with no evidence of infiltration of the pedicle or surrounding tissue, and the other an infiltrating neoplasm which behaves like the usual squamous-cell carcinoma but is associated with sarcoma-like spindle cells. Of the former group, four have been reported as metastasizing as sarcomas, while two of three of the latter group which have metastasized, have done so as squamous-cell carcinoma. This observation supports the concept that the sarcomatous

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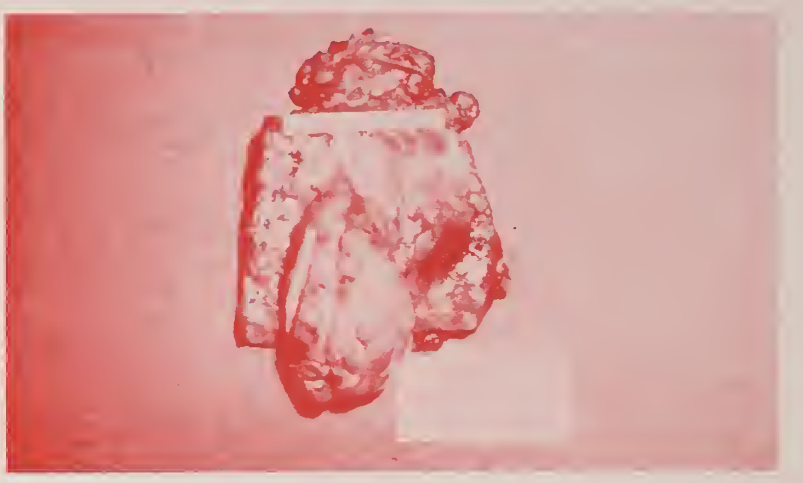

Fig. 2 — Gross specimen of distal esophagus and tumor removed at operation. The pedunculated mass has been detached from esophageal wall.

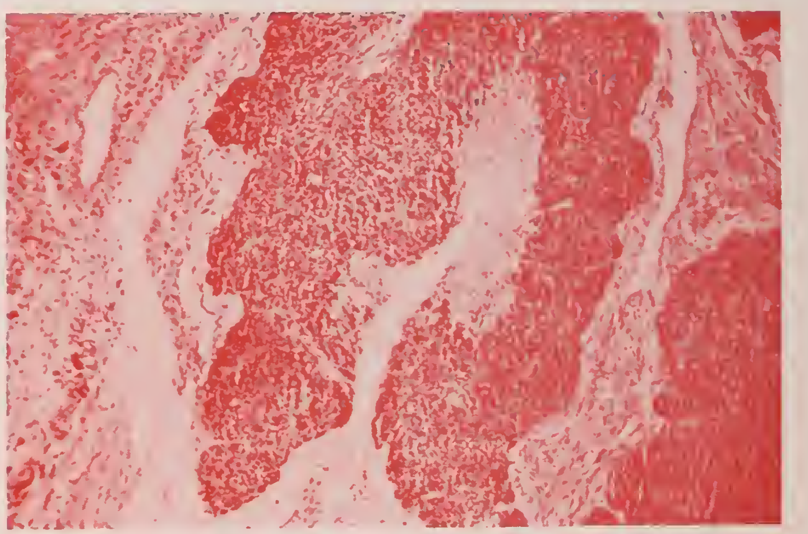

Fig. 3 — Photomicrograph showing anaplastic squamous cell epithelioma. (H and E 100 x)

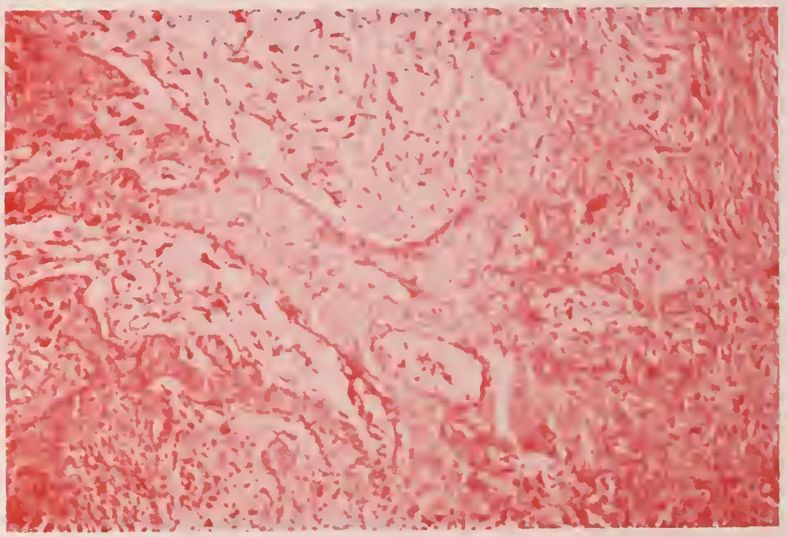

Fig. 4 — Photomicrograph showing well differentiated squamous cell epithelioma. (H and E 100 x)

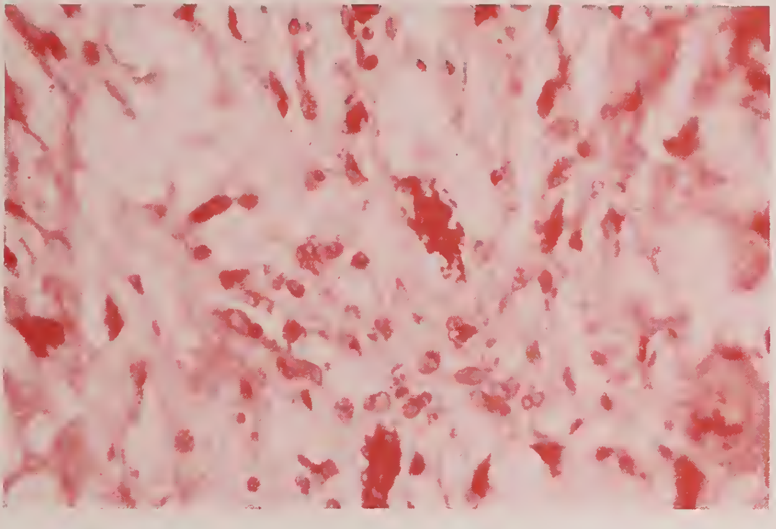

Fig. 5 — Photomicrograph of sarcomatous elements of tumor. Morphology suggests leiomyosarcoma. (H and E 430 x)

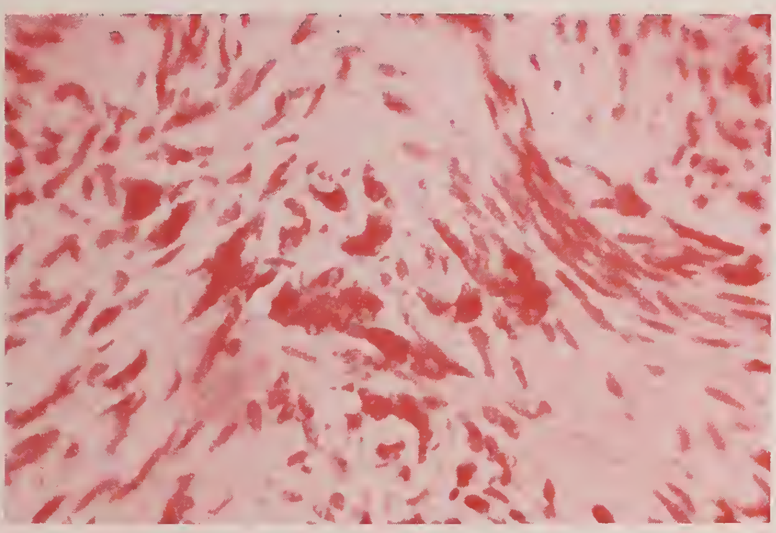

Fig. 6 — Photomicrograph of sarcomatous elements of tumor. Morphology suggests neurofibrosarcoma. (H and E 430 x)

element is a true neoplasm, and not simply a reaction of the connective tissue stroma as described with the group designated as pseudo-sarcomas.

Clinical Behavior

Whatever the origin of this tumor, the clinical behavior is unlike that of squamous-cell carcinoma of the esophagus Carcinosarcomas are usually polypoid tumors of the middle or lower third of the esophagus, most frequently occurring in middle-aged males. Dysphagia is the major symptom in most cases. Weight loss is common. Chest pain and vomiting are noted in a lesser but significant number of cases. The diagnosis should be considered when such a polypoid mass is demonstrated radiologically or when a biopsy of such a lesion shows squamous, or other epithelial carcinoma. At operation or autopsy, extensive local involvement and

Continued

metastases are much less common than with squamous-cell carcinoma of the esophagus. On the basis of experience with the few patients with this tumor who have been operated upon to date, it is suggested that the tumor has a better prognosis than the usual epithelial tumor of the esophagus, and that less extensive surgery is necessary.

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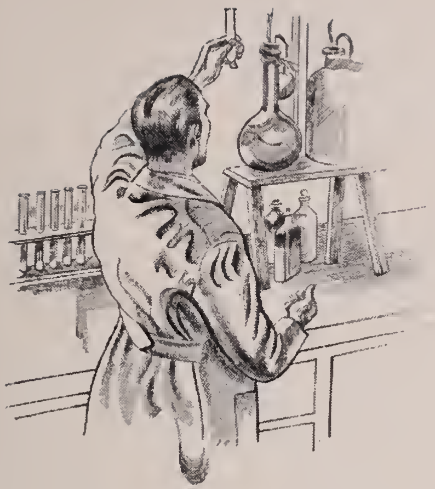
Progress Note

The nurse was drawing blood from an apprehensive patient and was using her most gentle, tender technique. When the procedure had been accomplished the patient looked at the nurse, and in a very sweet and tender voice said, "You have such a gentle touch, you would have made a wonderful safe-cracker."

The world is my country, all mankind are my brethren, and to do good is my religion.—Thomas Paine

Facts that are not frankly faced have a habit of stabbing us in the back.
— Harold Bowden

We have forty million reasons for failure, but not a single excuse. — Kipling



Clinical Path Conference

Pancreatic Carcinoma and Cardiovascular Complications*

In January 1963, a 49-year-old woman was admitted to the Charles T. Miller Hospital with a three-week history of gnawing midepigastric pain occurring in the midafternoon. The pain, which was alleviated by antacids, tended at night to radiate into the back. There was no vomiting or melena. A duodenal ulcer had been diagnosed roentgenographically in 1958. The family and occupational histories and the systemic review were noncontributory.

Physical examination revealed only vague midepigastric tenderness. The level of hemoglobin and the total and differential leukocyte counts were normal; urinalysis revealed no abnormalities. The serum amylase was 138 units, and the test for two-hour urinary excretion of amylase yielded 173 units/hr. Serum electrolytes were at normal levels. Roentgenographic examination showed that in one segment of the small bowel there were changes compatible with a localized enteritis. The patient was discharged without any specific therapy.

She was readmitted eleven months later because of shifting abdominal pain of two weeks' duration. On the morning of this admission the patient had developed pain in the right lower abdominal quadrant, weakness and diffuse diaphoresis. Physical examination revealed mild abdominal tenderness in both lower quadrants. Results of laboratory studies were within normal limits. Roentgenograms of the thorax, upper gastrointestinal tract, small bowel and colon gave negative results. An intravenous pyelogram was interpreted as negative. The symptoms gradually receded and the patient was discharged on the sixth hospital day.

One week following discharge from the hospital, the patient noticed insidious development of pain and swelling in the posterior aspect of the left leg, associated with redness and swelling. She was admitted to the hospital for the third time. Physical examination revealed pain, swelling, and erythema over the left medial malleolus. Determinations of the concentration of hemoglobin, the total and differential leukocyte counts, and the levels of blood urea nitrogen and uric acid were normal, as were agglutinations for typhoid and paratyphoid organisms. The L.E. clot test gave negative results. Thrombophlebitis was diagnosed, and this condition

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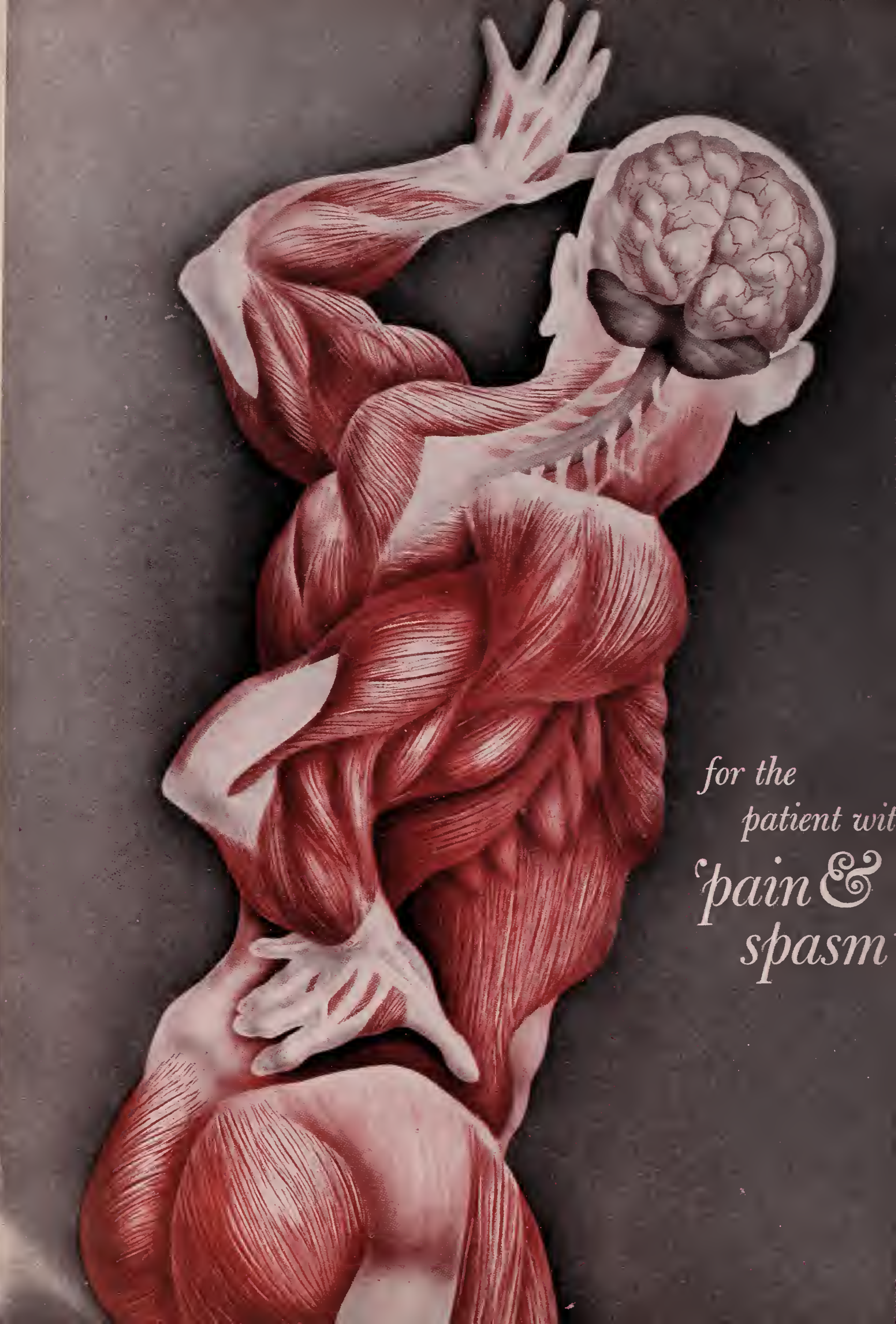
*See title for index purpose at end.

This study supported by Research Grant HE 05694 and Research Training Grant 5 T1 HE 5570 of the National Heart Institute, United States Public Health Service.


for the
patient wit
‘pain &
spasm

pain *is almost invariably a presenting symptom in cases of skeletal muscle* *spasm*

In some instances, the pain subsides on relaxation of the muscles in spasm. In others, relaxant therapy alone fails to give adequate relief, and supplementary analgesia (and possibly sedation) are indispensable, as in cases of:

provocative pain, when muscle spasm is triggered by some painful underlying musculoskeletal defect.

residual pain, when relaxation of severe spasticity leaves a degree of myalgia that tends to reinvoke spasm.

severe pain, when the degree of pain is such as to cause persistence of symptoms in spite of relaxant therapy.

emotionally aggravated pain, when anxiety or agitation creates tension that thwarts the efficacy of both relaxant and analgesic medication.

In such cases, ROBAXISAL and ROBAXISAL-PH have proven highly effective in assuring decisive and comprehensive relief. The ROBAXISAL formula—of ROBAXIN (methocarbamol), the potent muscle relaxant, together with aspirin, the time-tested and proved analgesic—produces higher plasma salicylate levels than equivalent doses of aspirin alone, and serves effectively to control both spasm and pain. ROBAXISAL-PH's combination of ROBAXIN (methocarbamol) with the analgesic-sedative ingredients of the PHENAPHEN formula—including phenobarbital—helps additionally to ease apprehension.

ROBAXISAL®

Robins

Each pink-and-white laminated Tablet contains:

ROBAXIN (methocarbamol, Robins)	400 mg.	Aspirin (5 gr.)	325 mg.

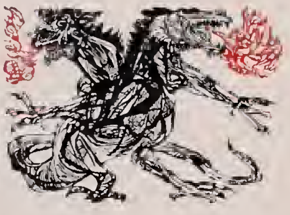
U.S. Pat. No. 2770649

ROBAXISAL®-PH

Each green-and-white laminated Tablet contains:

ROBAXIN (methocarbamol, Robins)	400 mg.	Phenacetin (1½ gr.)	97 mg.	Hyoscyamine sulfate	0.016 mg.
		Aspirin (1¼ gr.)	81 mg.	Phenobarbital (⅛ gr.)	8.1 mg.

(Warning: May be habit forming)



"PAIN & SPASM"
– a two-headed dragon!

ROBAXISAL and ROBAXISAL-PH are indicated in strains and sprains, painful disorders of the back, "whiplash" injury, myositis, pain and spasm associated with arthritis, torticollis, and headache associated with muscular tension.

Side effects such as lightheadedness, slight drowsiness, dizziness and nausea may occur rarely in patients with intolerance to drugs, but they usually disappear on reduction of dosage.

Contraindicated for patients hypersensitive to any component of the formulations. There are no specific contraindications to methocarbamol, and untoward reactions are not to be expected.

A. H. ROBINS CO., INC., Richmond 20, Virginia

subsided with bed rest and the application of heat. The patient was discharged after two days of hospitalization.

The final admission occurred one month later, February 10, 1964, when massive phlebitis of the entire left lower extremity became evident. This condition had existed for six days, but it had been mild until two days before admission. Ten days before the final admission, transient signs of phlebitis of the arm occurred at the site of injection for the intravenous pyelogram which had been performed on December 4, 1963.

In the days following the final admission, the phlebitis of the left lower extremity gradually improved with elevation, hot packs and anticoagulants. After about ten days of this regimen, the signs and symptoms relative to this extremity improved considerably, but the upper abdominal pain re-

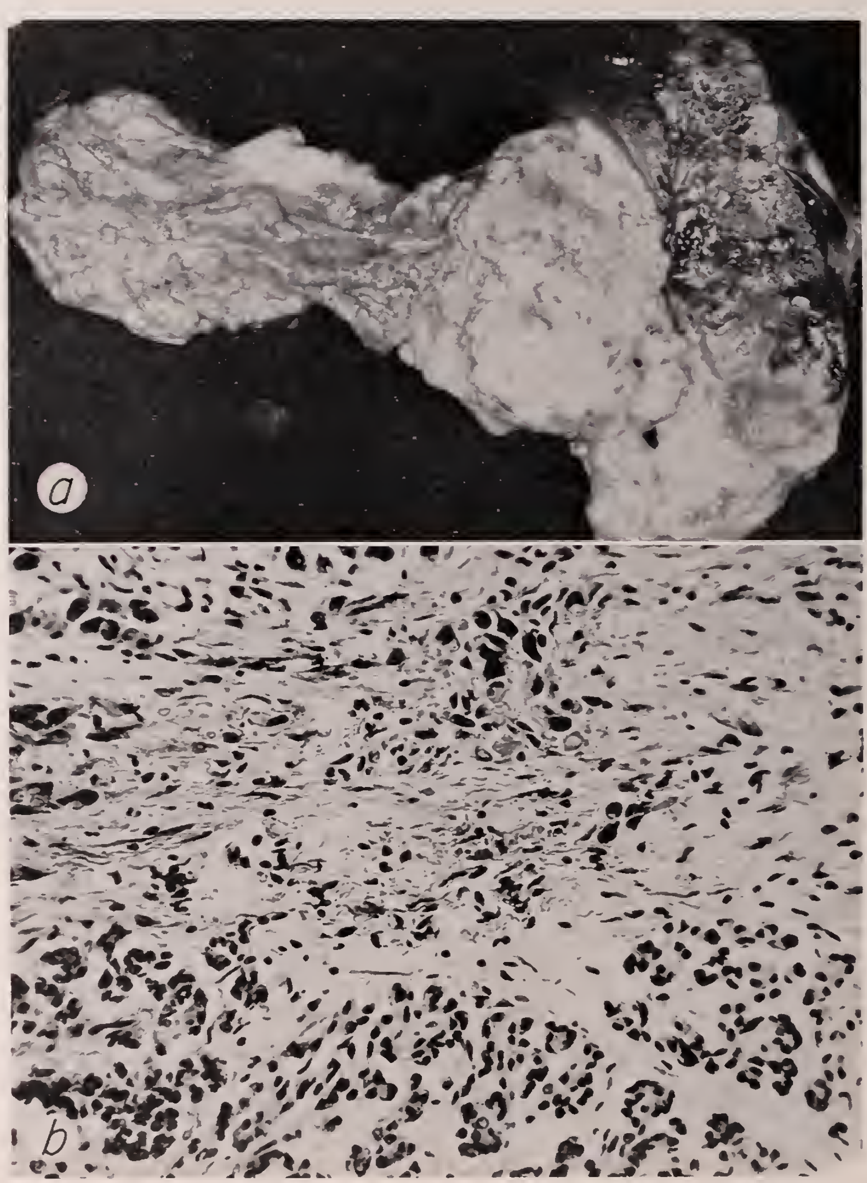


Fig. 1 — *(a)* Pancreas and spleen. Carcinoma involving tail of pancreas and invading the adjacent spleen. *(b)* Photomicrograph of pancreas. Beside a zone of intact pancreatic tissue is adenocarcinomatous tissue. H & E; X 220.

curred. This was described as a sensation of "gas or crampiness," was not relieved by antacid therapy, and seemed to radiate around both sides to the back. The patient said it was *not* similar to the ulcer pain noted in 1958. During this hospitalization the abdominal pain became progressively more severe; in spite of continuous anticoagulant therapy, new small segments of phlebitis in her hands and lower legs developed. A surgical exploration of the abdomen was done to investigate the severe abdominal pain. A few days after the operation, signs of impending gangrene of the right foot were noted, following which the patient's general condition deteriorated. On the thirtieth postoperative day, gangrene of the toes of the left foot appeared, and massive edema of both lower extremities had developed. The patient died 54 days after being admitted to the hospital for the fourth time and 14 months after the first admission.

Discussion

Visceral Malignancy

In a patient presenting with ill-defined abdominal complaints and recurrent thrombophlebitis, one strongly considers the possibility of visceral malignancy as the primary pathological process. The concept that patients with visceral carcinoma have an increased incidence of thrombophlebitis, first emphasized by Trousseau in 1861,[1] implies that there is some abnormality in the delicate balance between procoagulant and anticoagulant factors in the blood, or that some humoral factor exists which predisposes to venous thrombosis. In studying the validity of such a concept, it is of course necessary to exclude cases in which venous thrombosis occurs as a direct mechanical effect of a tumor, such as thrombosis of a renal vein or of the inferior vena cava in cases of carcinoma of a kidney. That distant venous thrombosis unexplained by direct mechanical factors has a tendency

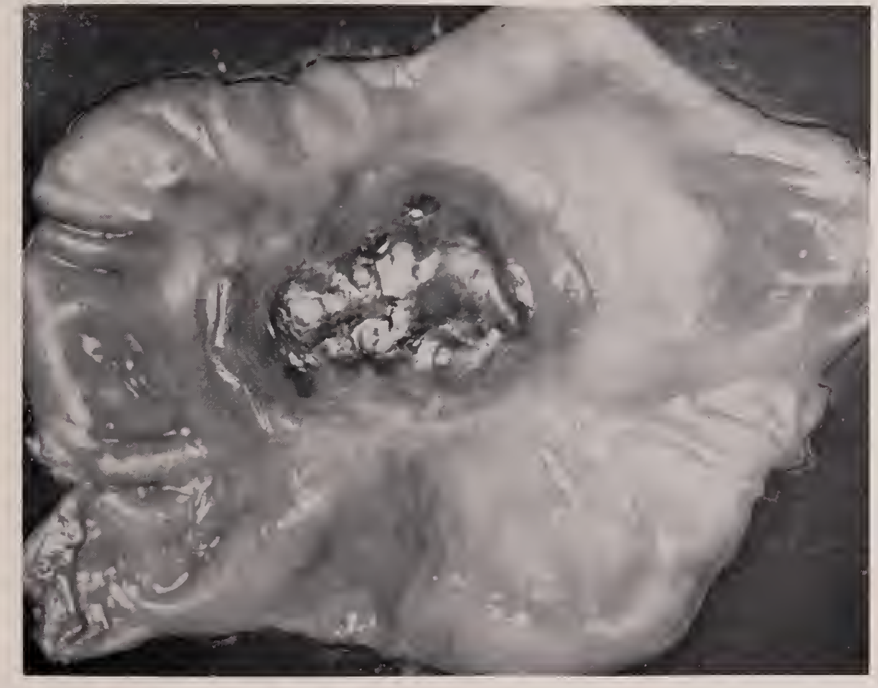


Fig. 2 — Interior of stomach. Ulcerative lesion representing extension into wall of stomach from primary carcinoma in tail of pancreas.

Continued

to occur in patients with visceral carcinoma appears established,[2] although not all investigators are agreed that an increased incidence exists, as compared to patients without malignancy.[3] It also appears that carcinoma of the pancreas is not the most common type of malignant tumor which predisposes to recurrent thrombophlebitis, as was commonly assumed, but rather that bronchiogenic carcinoma in males and genital malignant tumors in females have greater tendencies than does pancreatic carcinoma to underlie distant thrombophlebitis.[4]

Thrombosis Without Inflammation

Of the many concepts which have been proposed to explain the mechaism by which venous thrombosis occurs distant from malignant tumors, the more plausible at present include those of acceleration of thromboplastin generation on the basis of increased levels of the antihemophiliac factor in the blood and that of increased levels of antiplasmin or antiplasminogen in the plasma. The clinical suspicion that a case of thrombophlebitis may be secondary to visceral carcinoma is suggested by the finding of venous thrombosis with little inflammatory reaction around the vein, both by clinical examination and biopsy, as distinguished from the idiopathic thrombophlebitis or that seen in thromboangiitis obliterans.

In the patient under discussion, the duration of the symptoms and the character of the pain would suggest the possibility of carcinoma of the pancreas. The findings on the second admission are not readily explained, but the possibility of mesenteric thrombosis involving a small segment of bowel, which spontaneously relented, might be considered. The terminal gangrene of the legs is not readily explained by venous thrombosis alone, although reflex arterial spasm has been postulated to account for such findings.

Pathologic Aspects

Primary Carcinoma of Pancreas

The necropsy confirmed the observations made at the time of surgical exploration that there was a primary carcinoma of the tail of the pancreas (Fig. 1) with direct extension to the adjacent stomach and spleen. The tumor had invaded the stomach to the degree that the mucous membrane was ulcerated (Fig. 2). Metastases were found in the liver, left kidney, and lungs. The inferior vena cava, the iliac, renal and ovarian veins, although not involved by tumor, were occluded by thrombi (Fig. 3). Organizing pulmonary embolism involved arteries of the middle lobe of the right lung and the upper lobe of the left lung.

Arterial Insufficiency

With respect to the clinical signs of arterial insufficiency of the lower extremities, the mitral valve was of dominant interest. This valve, although fundamentally of normal structure, was the site of vegetations (Fig. 4), which were deposited in continuity upon the atrial surfaces of the anterolateral commissure and adjacent segments of the anterior and posterior leaflets. Gray, friable, and quite firmly attached to the underlying valvular structure, the vegetative material measured up to 8 mm. in thickness. No destructive lesions of the mitral valve were present.

Histologic examination of the mitral valve at the site of attachment revealed that the vegetation was acellular and composed of platelets and fibrin. A minimal reaction was present in the underlying valvular tissue. The vegetation was interpreted as of the marantic type.

Embolic Phenomena

Embolic phenomena were observed in the left common iliac and in the right renal arteries (Fig. 5). Each of these vessels showed its lumen to be occluded by friable and gray material both grossly and histologically similar to that of the vegetations of the mitral valve. Histologically, no reaction to the occlusive material was identified, suggesting that embolism to these vessels had occurred only a short time before death.

It is assumed that the signs of arterial insufficiency of the lower extremities, which had been noted clinically, resulted from embolism of vegetations of the mitral valve to the lower femoral arterial system, an area which was beyond the level of dissection in the necropsy. This view

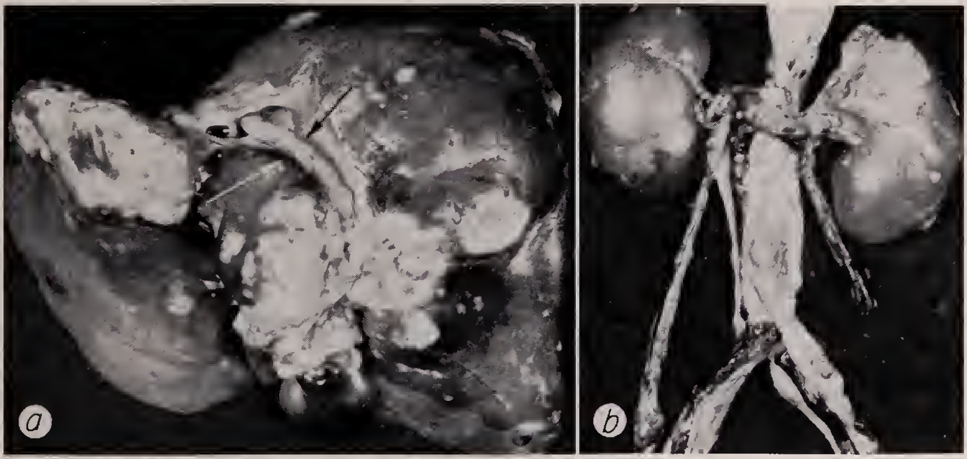


Fig. 3 — *(a)* Posterior aspect of liver. In the opened inferior vena cava there is a thrombus (between arrows). Also, metastatic carcinoma is present within the liver. *(b)* The kidneys and the great vessels of the abdomen. Thrombi are present within the inferior vena cava, the iliac veins, the left renal vein, and the ovarian veins.

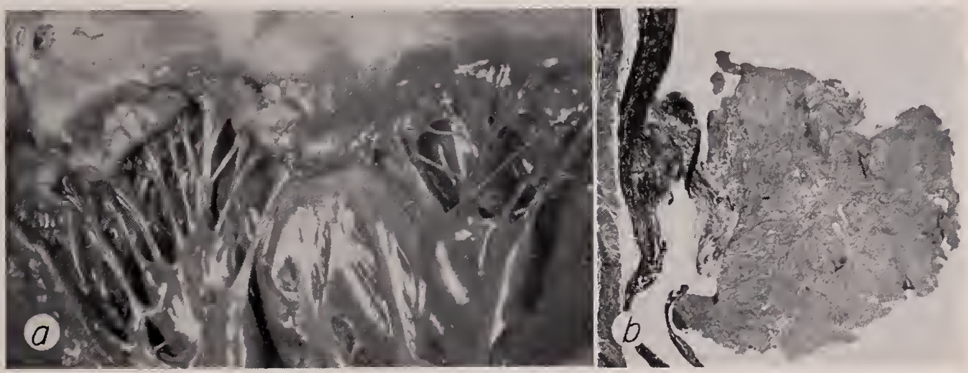


Fig. 4 — *(a)* Mitral valve. At the posteromedial commissure and at the adjacent anterior and posterior leaflets is vegetative material which is considered to be marantic in nature. *(b)* Photomicrograph of mitral valve showing vegetative material attached to the atrial surface of the valve. The vegetative material is acellular and is composed of fibrin and platelets. Minimal reaction in the valvular tissue. H & E; X 15.

Continued

is held in spite of the fact that the left common iliac artery was found to be occluded. It will be recalled that in this location no reaction was found to the emboli material. Had this occlusion been responsible for the clinical signs of arterial insufficiency in the left leg, one would have anticipated that sufficient time would have elapsed for a reaction to have occurred in response to the embolus. Infarcts found in the spleen and right kidney are also considered to have resulted from embolism of marantic vegetations of the mitral valve.

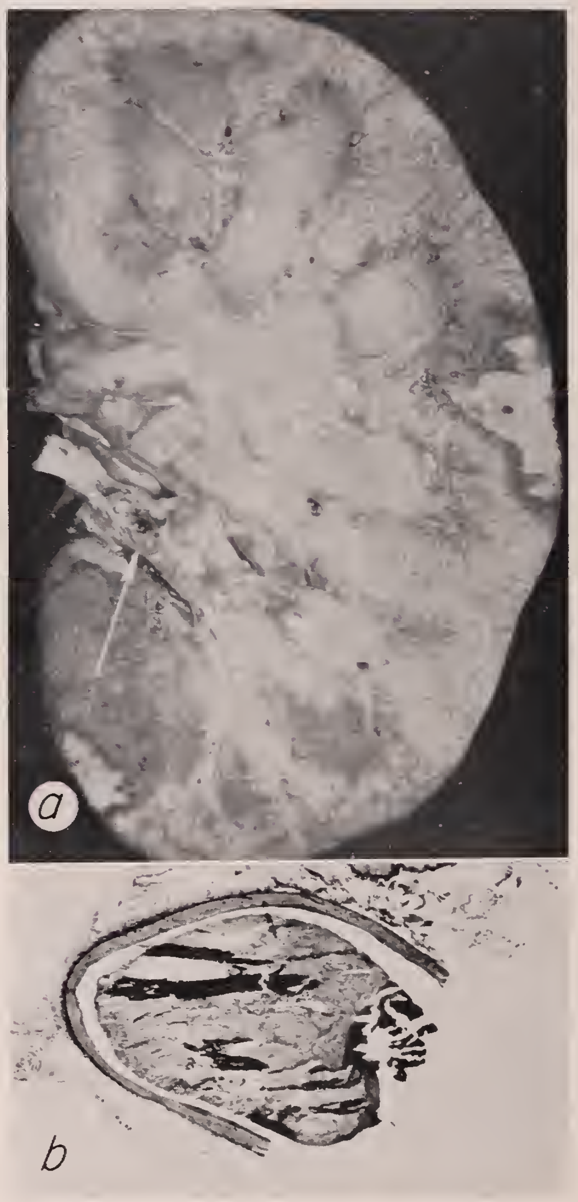


Fig. 5 — *(a)* Right kidney. At the hilum the renal artery is occluded by embolic material (arrow). Several infarcts are present in the kidney. *(b)* Photomicrograph of the right renal artery. The lumen is occluded by material similar to that composing the mitral valvular vegetations and is considered to be embolic from the mitral valve. No reaction is present to the embolus. H & E; X 10.

The case at hand exhibits two cardiovascular complications of visceral carcinoma, one generally recognized, the other more obscure.

Venous thrombosis (and complicating pulmonary embolism) like those which were present in this case, and readily apparent clinically, are now so well known as possible complications of a visceral carcinoma that the physician is alert to the possibility of such a carcinoma in any patient who presents with so-called idiopathic thrombophlebitis.

Marantic Vegetations

Less commonly recognized as being of clinical significance are the marantic vegetations that may develop upon the mitral or aortic valves in patients harboring a malignant tumor. The marantic vegetation, one of the several forms of nonbacterial verrucous endocarditis, has long been recognized as a condition apt to be encountered at necropsy in the debilitated subject. Its very name is derived from the wasted condition of the patient. It is, however, significant that some patients with visceral carcinoma develop marantic vegetations before a debilitated stage is reached. Moreover, once marantic vegetations develop, they may give rise to systemic embolism. In uncommon situations emboli derived from marantic vegetations may represent the first sign of illness in the patient with a visceral carcinoma.[5] At other times, as in the case presented, embolism from marantic vegetations may complicate the clinical state of the patient who presents with other signs and symptoms of visceral carcinoma.

As to the nature of the marantic vegetations, two schools of thought exist. One is that they represent simple deposits of elements of the blood upon the intact valve. The other opinion, based on the clear demonstrations of Allen and Sirota[6], is that the process primarily is one of nonbacterial alteration of valvular substance and that the vegetations form secondarily at sites of such alteration.

Final Diagnosis

1. Carcinoma of Tail of Pancreas.
2. Thrombophlebitis.
3. Marantic Endocarditis of Mitral Valve.
4. Systemic Arterial Embolism.

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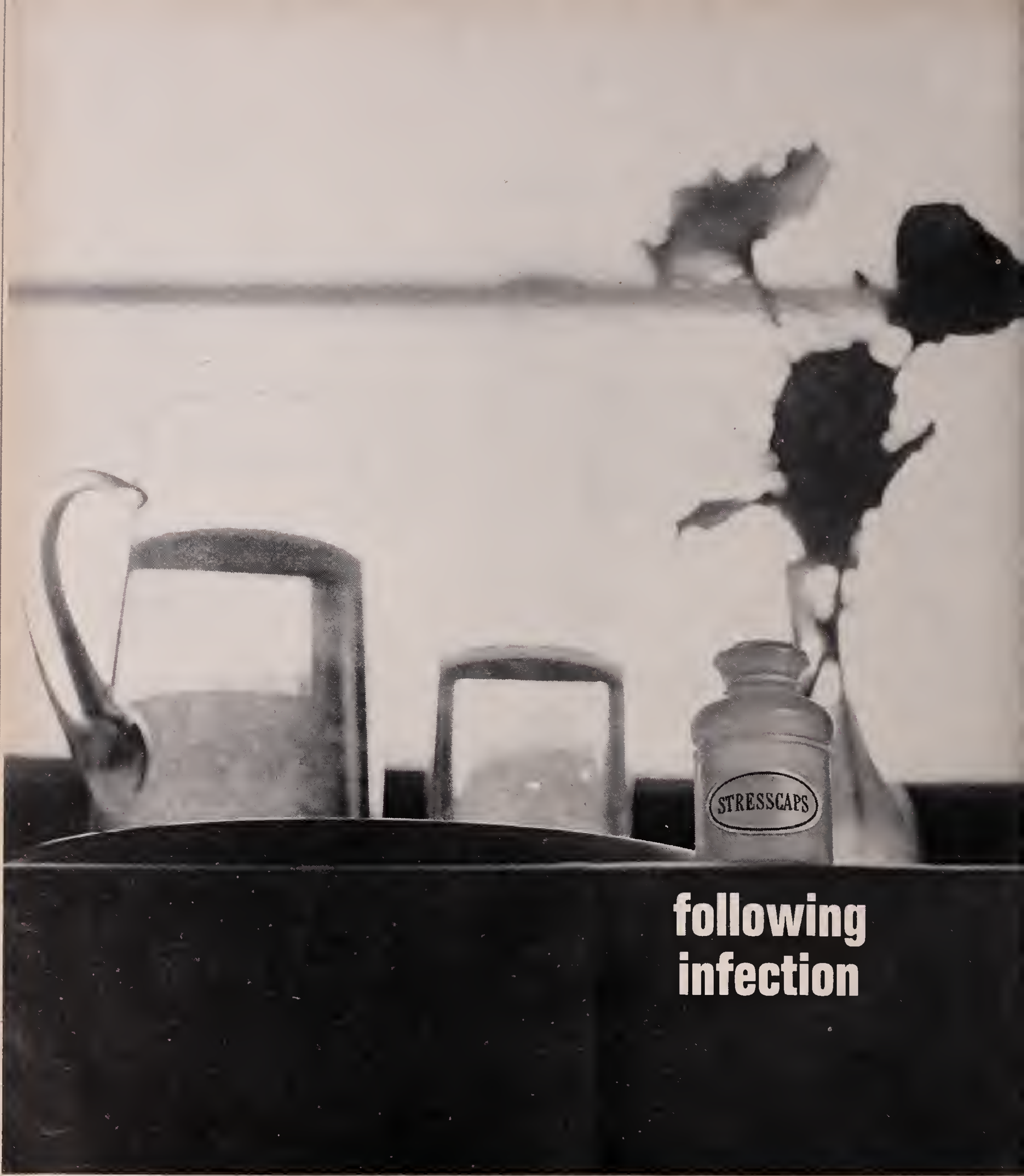

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Neuro-Pediatrics Conference

Parkinsonism*

The symptoms and signs characteristic of this disease were first enumerated by Parkinson in 1817, but the problem of etiology and satisfactory treatment has persisted through the years to the present. In the past decade a surgical approach to the alleviation of the symptoms of this disease has become established. The criteria that determine whether surgery will help are fairly definitive but must be evaluated for each individual patient. One must compare the patient's age and general physiological health with the degree of disability which he has. Even more significantly, the details of the patient's personality, family life, and social responsibilities may play a very important role in determining the ultimate care he is to receive.

Charles Olson:**

The patient is a 45-year-old Polish widow who has had symptoms of Parkinsonism for approximately 12 years. She had first noted a very mild nonspecific tremulousness in 1951, shortly after arriving in the United States, but attributed this to nervousness. In 1956, her chin developed a persistent tremor which subsequently spread within the succeeding year to involve her right arm and hand; however, she had no particular difficulty with this mild shaking until her husband's death in 1961. The anxiety produced by the loss of her husband considerably aggravated the tremor, and it has subsequently continued to worsen in spite of medication. At present her medications consist of artane 2 mg. three times a day, cogentin 2 mg. at bedtime, and benadryl 25 mg. three times a day. On this regimen her tremor is partially relieved, enabling her to do housework; however, she is unable to feed herself with her right hand.

The past history of the patient is particularly unremarkable in regard to childhood diseases or influenza. The one exception was a penetrating wound of the right groin incurred at age nine by a fall onto a picket fence from a tree. Her three-month hospitalization for this injury was marked by a very septic, stormy course.

On physical examination the patient had a moderately severe 5-6 cycle/second tremor involving the right upper extremity and chin, and also to a less degree the right leg and tongue. There was a moderate lack of

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*Sponsored by the U. S. Public Health Service Grant N2502A63. Co-ordinators for the project are Dr. Robert W. ten Bensel, in Pediatrics, and Dr. Robert Soll, in Adult Neurology.

**Student doctor, University of Minnesota Medical Center.

Continued

expression in her face, and during walking, the right arm was held motionless at her side. There was no rigidity in her extremities except for mild cogwheel rigidity of her right arm. Also a weakness of convergence of the eyes was noted. Otherwise the physical examination was within normal limits.

Surgery to improve her condition has been offered, but she has persistently refused.

Dr. Robert Soll:*

Dr. Borowicz, would you give us your impression of the patient, and how her condition has changed during the past several years while she has been under your care?

Dr. Leonard Borowicz:**

Her tremor started eight years ago during her last pregnancy. There were financial problems. Her husband, a machine-operator, was an aggressive, well-meaning fellow, but he limited himself to the responsibility of merely providing for his family. As time went on, it was noted that the patient had a definite pillrolling tremor and a lack of facial expression. Without further neurological consultations I started her on anti-parkinson medication.

Her husband, although having had rectal bleeding for a year, had never come to the office for an examination. He had a stage 3 carcinoma of the rectum and died within a year. She was then left without any hospitalization or means of support except for what the welfare would offer. Whether this was a precipitating factor or not, her tremor became markedly worse during that period of time.

I do not know the grade level of basic education this lady completed in Poland, but I suspect it was not much beyond the fourth grade. She may understand that there is a possibility of her being helped by surgery, but she is also a little fearful. However, with the help of two ladies who speak Polish in the neighborhood and whose tremor has been helped by surgery, this fear might be overcome. If we conclude that she should be given the opportunity to have an operation, they might help her agree to one.

This woman shakes so violently that she is going to be incapable of supporting herself much longer. Soon she will not even be able to clothe herself, although she is only 45 years old.

Dr. Soll:

Dr. Brantner, your opinion of the psychological status of the patient would be very valuable in determining how we should approach her regarding further treatment.

Dr. John Brantner:***

Psychological testing of the patient was extremely difficult, as she was exceedingly uncomfortable and tense. Since she speaks and reads no English, many standard tests were impossible and her daughter was not a very objective interpreter. During the nonverbal tests, errors made by the patient exasperated the daughter, and she chided her mother for making errors. The patient is probably in the lower 5% of the population intellectually. I found some very minor suggestive signs of organic brain damage; however, this again was not conclusive because of testing difficulties. During the tests the tremor became much more gross. I tried the nonverbal tests; but as the items became progressively more difficult, the tremor became worse, and this necessarily prevented the use of pantomine paper and pencil tests. In short, there is a language barrier, a cultural barrier, and a probable intelligence barrier. She is a frightened woman in the total medical setting.

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*Adult Neurology, University of Minnesota Medical Center.

**Family Physician.

***Clinical psychologist, University of Minnesota Medical Center.

Dr. Soll:

It is important also to know the patient's family problems. Does she need to work to support her family? Does she have children who are dependent on her emotionally? Our plans for her future will be influenced considerably by these facts. Miss Kretchmer, would you tell us your opinion about these questions?

Miss Helen Kretchmer:*

I have had some of the same problems as Dr. Brantner. I did feel distinctly handicapped in that the daughter seemed to translate poorly and was most responsive when asked about herself. She interprets for her mother only rarely, since the patient seldom goes beyond the store, her friends, or her church. She was even reluctant to come to the hospital in 1957 because of her language problem.

The family currently consists of the patient and her daughters, ages 18, 13 and nine years. The oldest, a chubby, stolid-appearing girl with bleached hair, is a senior in high school, maintaining a C average with a few B's. Her plans are to study cosmetology. The family financial situation has not concerned her greatly since she has felt that a course in cosmetology was not too expensive. She has been in a school choir since the fourth grade and is now a soprano in a select high school chorus. The 13-year-old daughter is in the eighth grade and the youngest in the fifth grade. The family is well associated with their church, a Polish Catholic Church, and the children have participated in youth groups there.

The family came from near Warsaw, Poland, via Germany in 1951. The sponsor for their immigration to the United States was a staunch friend, and they still occupy four rooms in her home, which is in a Polish neighborhood in a Catholic parish. The family have their own vegetable garden, and the children help their sponsor with her flowers. The closest relatives are cousins of the father who live in Gary, Indiana, whom one of the children visited this past summer.

The family income is $228.20 Social Security for the mother and the two children under 18. The patient also has been working part time nights as a cleaning woman, earning $1.69 an hour to supplement their income. They applied for Aid to Dependent Children in 1962, but their application was denied because the family income was too great at that time.

One of the major family difficulties, besides the limited income, seems to be the patient's dependence on her children for her language problem. According to a friend, she has been very depressed, or at least not well motivated, since her husband's death. This fact does not appear to create significant problems for the children now, but may later. Evidently they

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*Supervisor and assistant professor of Social Service, University of Minnesota Medical Center.

Continued

do not now forsee some of the difficulties the mother might create when they marry or take jobs.

There are Americanization and English language classes available under the Board of Education at the Northeast Community Center, but the patient has not availed herself of them. The Assistant Director of the Community Center, Mr. Holloway, has known the family for years through the camp program.

Mr. Joe Holloway:*

My contact with the family has been mainly with the children, less with the mother. The children have attended our camp, the oldest child being the first in 1956. She enjoyed the camp tremendously. The second child was at camp last year. It became fairly evident then that as a result of the low family income, the camping fee would have to be supplemented with Campership. This child volunteered that she herself would pay the fee through babysitting, doing chores, and cleaning around the neighborhood in various homes. She did this and attended camp, enjoying it very much.

I had the opportunity of seeing the husband before he died. He seemed to be a fairly normal, active gentleman, very devoted to his family, and wanting them to have some of the better things in life. He was anxious for his children to go to camp. The youngest member of the family is interested in going, although she is not yet old enough.

At this point in the conference, the patient was brought into the room. She was very apprehensive as manifested by a marked increase in the degree of tremor in her right arm. After the physical findings, as enumerated in the history, were demonstrated to the group, the patient again left the room.

Dr. Soll:

This demonstrates the emotional aspect of Parkinsonism very dramatically. Her tremor isn't normally quite this marked. When we saw her in clinic, the uncertainty and apprehension were less so, but now, under this stressful situation, the tremor is almost twice as great.

Dr. Brantner:

A similar thing happened during the psychological testing. With easy tasks she was able to write legibly, but as the tasks got harder the tremor became much more marked.

Dr. Soll:

Her main difficulty right now is the tremor. One can demonstrate, of course, cogwheel rigidity, to be expected with this tremor; fortunately there is not a great degree of rigidity per se.

Dr. James Story:**

I would first like to emphasize that surgery does not cure Parkinsonism, but it often relieves some of the symptoms. I think the case at hand is unfortunate in that this patient is not interested in having surgery. For a number of years she has had symptoms of tremor and mild rigidity, which have been slowly progressive. Furthermore, her disability has been limited in that the tremor involves only the right side of her body. These manifestations of tremor and rigidity would make her an excellent surgical candidate. The fact that she has very minimal akinesia is also in her favor. I predict that she would have about a 95% chance of being relieved of her tremor. The longer we wait, the more severe these manifestations will become.

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*Assistant Director of Northeast Neighborhood House, Minneapolis.

**Assistant Professor of Neurology, University of Minnesota Medical Center.

Dr. Soll:

Could you tell us about the complications and risks that would be involved in this surgery?

Dr. Story:

The most devastating complication of all is that she might die — but I think this is highly unlikely; the mortality of this procedure is 1% or less. There is a chance that she could be hemiplegic following the procedure, but there again I think chances are slight.

Dr. Soll:

Would you also estimate the possibility of the tremor returning, although the operation may be a success initially?

Dr. Story:

Parkinsonism is usually a rather benign disease, because it is a slowly progressive condition. When we do this operation we produce only a small lesion in the subthalamic region, so that sometimes it is necessary to repeat the operation. I think I would prefer this to making too large a lesion the first time and having a greater risk of complication.

Dr. James Moriarty:*

Does this patient have a postencephalitic type of Parkinsonism?

Dr. Soll:

We do not know. From the history we have not obtained any evidence of influenza or encephalitis. The patient did have an accident at the age of nine years though, in which she fell out of a tree onto a picket fence. A picket pierced her right groin, subsequently causing a severe infection and a very high fever. Whether or not this might be related to the illness is only speculation.

Dr. Moriarty:

Dr. Story, are your results better in those patients who have the postencephalitic type of Parkinsonism?

Dr. Story:

There are some people who would de-emphasize the arteriosclerotic type of Parkinsonism; however, I do not agree with them. Surgically, the best results occur in those patients with a slowly progressive disease, who are physically young. This patient fits these criteria.

Dr. Michael Blaw:*

If the surgery were successful, do you think, Dr. Brantner, that the patient would be capable of learning, in view of the language barrier?

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*Assistant Professor of Neurology, University of Minnesota Medical Center.

Continued

Dr. Brantner:

Certainly I am glad to hear Dr. Borowicz say that she probably had about a fourth grade education, since that would correlate well with the psychological test. Most fourth graders do learn English, and I think most could also learn a second language; however, it would not be as easy as teaching a very bright person a second language.

Dr. Blaw:

It has been said that a child's brain has a special capacity for learning language, which the adult may lose. The child's brain is immature in many ways; but it is hard to believe that any function as complex as language could be present in an immature brain to a greater extent than in an adult. Dr. Brantner could confirm the fact that during periods when a child is learning a new motor task, like walking, for example, his speech will plateau for awhile. I think this partially explains the adult problem; adults have so much to be concerned about that they cannot devote as much time to acquiring a new language as the child.

Dr. Borowicz:

Two of her little girls need her maternal support and care, but I can see nothing for the patient but the prospect of progressive deterioration, mentally and physically. Soon she will not have the capacity to perform as a mother. I think that her case has reached a point where we may have to help her make a decision. Dr. Story, do you think that it would be morally right to have a neighborhood woman, who speaks Polish and who also has had this same operation, try to encourage the patient to accept surgery?

Dr. Story:

I would encourage you to recommend that the operation be done. I do not believe it would be unethical to have a friend speak to the patient, if she were willing to do so. Such a talk could relieve the patient's anxiety about surgery.

Dr. Soll:

At this point, I would like to comment on the drug therapy for Parkinsonism. Usually a basic drug such as artane or pagitane is first introduced. Artane may be given in a dosage of 1 or 2 mg. three times daily, or pagitane 1¼ mg. two or three times daily. Both of these drugs have a considerable suppressive influence on rigidity and will decrease the tremor. In addition, both act as mild cerebral stimulants without risk of having a pressor action which could be detrimental in arteriosclerotic patients. Akineton and kemadrin are likewise similar drugs which could be used as a basic medication. A useful supplement, such as cogentin, given as a 1.0 mg. tablet at bedtime, may then be added. Cogentin tends to have a cumulative effect and acts as a powerful muscle relaxant. Synthetic antihistamines such as theophorin or benadryl might also be added to the drug regimen. Their main purpose is to produce a feeling of well-being and tranquility in the patient, but they have other than this no effect on the symptoms and signs of Parkinsonism. You will note that our patient today is receiving a combination of a basic drug, artane, supplemented by cogentin and benadryl. She is probably taking close to what would be considered a maximum amount of medication without developing significant side effects from the drugs.

Dr. Story:

I would like to ask Dr. Borowicz' opinions concerning the effects that these drugs have had on her tremor in general, as well as on her emotional state.

Dr. Borowicz:

She has probably benefited from the drugs as far as controlling her emotional tone and stability is concerned. The exceptions have been during periods of real stress, such as when her husband died or when financial insecurity threatened. However, the drugs have not adequately controlled her tremor.

Dr. Soll:

If there is no further discussion, I would like to summarize. We have a 45-year-old mother with a significant degree of disability due to Parkinsonism which we know will continue to progress. She shows a great amount of anxiety and a fear of people, which have probably been accentuated by a language difficulty and the insecurity caused by her husband's death. She has a family of three children without the benefit of a father to help care for them. Since the Parkinsonism symptoms have been relatively limited to one side of her body because she is relatively young, this patient is an excellent candidate for surgical amelioration of her condition. It is felt that such relief of her symptoms would allow her to remain an active, contributing mother to her family and to the community in which she lives. By working through her family physician, Dr. Borowicz, the social workers, and her friends, it is hoped that we may be able to better explain to her the benefits that surgery has to offer.

Robert Soll, M.D.
University of Minnesota Medical Center

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Participating in conference: the patient's family physician, Dr. Leonard Borowicz; Charles Olson, student doctor; Dr. John Brantner, clinical psychologist (University of Minnesota Medical Center); Miss Helen Kretchmer, supervisor and assistant professor of social service (University of Minnesota Medical Center); Mr. Joe Holloway, Assistant Director of Northeast Neighborhood House; Dr. James Story, assistant professor of neurosurgery (University of Minnesota Medical Center); Dr. James Moriarty, assistant professor of neurology (University of Minnesota Medical Center); Dr. Michael Blaw, assistant professor of neurology (University of Minnesota Medical Center); and Dr. Robert Soll, chairman, adult community services (University of Minnesota Medical Center).

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Prevention of Bacteremia after Oral Surgery

WILLIAM J. MARTIN, M.D.*
ALEXANDER SCHIRGER, M.D.*
Rochester, Minnesota

From time to time, members of our group have presented data on the application of antimicrobial agents in infectious problems of dental origin.[1-6] Our interest has been centered chiefly on attempts to prevent bacterial invasion of the blood following oral surgical procedures.

Use of Phenoxymethyl Penicillin Preoperatively in Normal Persons

In 1957 members of our group initiated a series of studies designed to compare the incidence of bacterial invasion of the blood of patients undergoing oral surgical procedures without receiving any antibiotic beforehand with that of patients who were given phenoxymethyl penicillin by mouth before operation. We were interested in determining whether penicillin in this form, without adjunctive parenteral administration of penicillin G, would be an effective prophylactic. Also we wished to know whether the agent would suffice when given 24 rather than 48 hours before operation.

Patients and Dosage

Samples of blood for cultures were obtained from 127 patients immediately after oral surgical procedures.[2,3] Another sample was obtained 18 hours later. None of the patients had cardiovascular defects which would make them susceptible to the development of endocarditis or endarteritis. Fifty of these patients, referred to as "group A," did not receive any antibacterial agent before operation. An additional 50 patients, referred to as "group B," received 4,000,000 units of phenoxymethyl penicillin preoperatively; 1,000,000 units or 600 mg. of the drug was given every six hours for a total of four doses, and surgery was undertaken within four hours after the last dose. This amount of penicillin approximates the preoperative dose recommended by the American Heart Association for patients with cardiovascular defects that would make

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*Section of Medicine, Mayo Clinic and Mayo Foundation, Rochester, Minnesota.

Continued

them susceptible to the development of bacterial endocarditis or endarteritis. However, the Association had recommended that a dose of this size be given in part by mouth and in part by injection, and also that treatment begin approximately 48 hours before operation. The schedule followed in this study appeared to be more applicable to the practice of oral surgery at the Mayo Clinic, where it is sometimes difficult to begin treatment more than 24 hours before operation. The remaining 27 patients, referred to as "group C," received 500,000 units or 300 mg. of phenoxymethyl penicillin every six hours for four doses, for a total preoperative dose of 2,000,000 units of the antibiotic.

Surgical Procedures

The number and type of oral surgical procedures carried out on patients in the various groups are as follows. Of the 50 patients in group A, 12 had more than 15 teeth extracted, 23 had one to four impacted teeth removed, and one had a torus palatinus excised. Of the 50 patients in group B, 10 had more than 15 teeth removed, 29 had impacted teeth removed, and two had large cysts removed. Of the 27 patients in group C, four had more than 15 teeth removed, 20 had impacted teeth removed, and one had a sequestrectomy for osteomyelitis.

Results

From 27 of the 50 patients in "group A," who had not received an antibiotic, cultures of blood drawn immediately after operation were positive (Table 1). Ten of these positive cultures involved streptococci of the mitis group, and one yielded Staphylococcus aureus. From eight of the 50 patients in "group B," who had received 4,000,000 units of phenoxymethyl penicillin preoperatively, cultures of the blood drawn immediately after surgery grew bacteria, but none yielded streptococci of the mitis group. Glaser and co-workers[7] previously had found a marked decrease in the incidence of alpha hemolytic streptococci in their patients who had received penicillin before dental extraction. Also, Hirsch and associates,[8] when they considered the alpha and gamma streptococci alone, obtained a reduction in the incidence of bacteremia from 34 to 15 per cent with use of penicillin before dental operation. When a dose of 2,000,000 units was used for the 27 patients in "group C," cultures of blood immediately after surgery from five were positive; the blood from one of these five yielded Streptococcus mitis. Also in this group the incidence of positive cultures of blood drawn 18 hours postoperatively was significantly increased. With the report that the culture was positive for Streptococcus

TABLE 1

Phenoxymethyl Penicillin: Blood Cultures After Oral Operation With and Without Preoperative Administration (127 Patients)

	Blood drawn for cultures					
	Group A (50 controls)		Group B* (50 patients)		Group C† (27 patients)	
	At operation	18 hr postoperative	At operation	18 hr. postoperative	At operation	18 hr. postoperative
Positive cultures						
Str. mitis	10				1	
Nonhemolytic Str.	1					
Staph. aureus	1	1				
Coagulase-negative Staph.	7	2	3	1	3	2
Peptococcus		1				
Unidentified gram-negative bacillus	1			1		
Corynebacterium	7	1	5	1	1	2
Total cultures						
Positive	27	5	8	3	5	4
Negative	23	45	42	47	22	23

*4,000,000 units phenoxymethyl penicillin preoperatively.

†2,000,000 units phenoxymethyl penicillin preoperatively.

mitis, no more patients were added to "group C."

Comment

These data appear to indicate that phenoxymethyl penicillin when given in amounts of 4,000,000 units was as effective in decreasing the incidence of bacterial invasion of the blood after oral surgery as have been other forms of penicillin given on differing schedules by other investigators. They also appear to indicate that when 4,000,000 units of phenoxymethyl penicillin is to be given by mouth, this treatment need not begin until 24 hours before operation, rather than 48 hours beforehand.

Use of Phenoxymethyl Penicillin Preoperatively in Persons with Heart Murmurs

A second study was designed to investigate the effectiveness of phenoxymethyl penicillin in preventing bacterial endocarditis following oral surgery on patients having valvular defects that would make them susceptible to the complication.

Patients and Dosage

Fifty-two patients were selected for this study who had heart murmurs which had prompted the recommendation of the referring internist that prophylactic therapy with an antibiotic be instituted before oral surgery.[5] Phenoxymethyl penicillin was administered orally in amounts of 500 mg. every six hours for four doses preoperatively. Surgery was carried out within four hours of the fourth dose, and the medication was continued at the same interval for 48 hours postoperatively. Cultures were made with blood taken immediately after operation and again approximately 18 hours later.

Surgical Procedures

The surgical procedures were as follows: extractions and alveoloplasty, 17 patients; extraction and odontectomy, 17 patients; odontectomy only, nine patients; extractions, four patients; extractions, alveoloplasty, and removal of paradental cysts, three patients; removal of a root, one patient; and removal of infected teeth, one patient.

Results

The cultured specimens from eight patients were considered to be contaminated; this left 44 patients for microbiologic study. Only three of these 44 patients showed evidence of bacterial invasion of the bloodstream (Table 2). In one patient, coagulase-negative Staphylococcus aureus was found after five days in culture of blood obtained immediately after surgery, and Escherichia coli was recovered from blood obtained 18 hours postoperatively. Blood from a second patient yielded Escherichia coli after four days of incubation of samples obtained im-

TABLE 2
Phenoxymethyl Penicillin: Blood Cultures After Oral Operation With Preoperative Administration (44 Patients With Cardiac Valvular Defects)*

	Blood drawn for cultures	
	At operation	18 hr. postoperative
Positive cultures	1 Coagulase-negative Staph. aureus (after 5 days' incubation)	E. coli
	1 E. coli (after 4 days' incubation)	Unidentified gram-negative bacillus (after 5 days' incubation)
	1 Coagulase-negative Staph. after 8 days' incubation	No growth
Total cultures		
Positive	3	2 (of preceding 3)
Negative	41	

*Received 500 mg. every 6 hr. for four doses preoperatively, then every 6 hr. for 48 hr.

Continued

mediately after surgery, and an unidentified gram-negative bacillus was grown after five days of incubation of the samples obtained 18 hours postoperatively. In a third patient a coagulase-negative Staphylococcus was recovered after incubation for eight days of blood obtained after the operation, but cultures of blood obtained from this patient 18 hours postoperatively were negative. All 52 of these patients have had follow-up for a minimum of one year, and none has given evidence of subacute bacterial endocarditis.

Comment

The one-year follow-up would appear to be adequate to exclude the occurrence of bacterial endocarditis etiologically related to the oral surgical procedure on which this study was based. On the basis of these experiences, a further trial of a similar mode of prophylaxis in a larger group of patients appears justified.

Discussion and Conclusions

In accord with our own experience, Hirsch and his associates[8] had been unable to find a correlation between the incidence of positive blood cultures and the state of oral hygiene or the number of teeth extracted. McEntegart and Porterfield,[9] Von Lautenbach,[10] and Gutverg and Haberman[11] likewise were unable to find a correlation between the occurrence of postoperative bacteremia and the status of the patient's oral hygiene at the time of the operation.

We have been unable to detect significant absence of bacterial invasion of the blood related to specific surgical procedures, in agreement with the observations of Korn and Schaffer[12] in 100 consecutive cases in which blood samples were obtained after various oral surgical procedures. Therefore, we have administered the prophylactic antibiotic regimen regardless of the type of surgical procedure contemplated.

At present we are studying a group of patients to whom erythromycin has been administered before oral surgical procedures. Erythromycin currently appears to be the best substitute for patients who cannot accept penicillin. However, a microbiologic difficulty inherent in this study is the unavailability of a substance akin to penicillinase which, on its addition to the culture medium, will neutralize the antibiotic contained in the blood sample and thereby prevent inhibition of bacterial growth.

We are aware of data indicating the isolation of penicillin-resistant gram-positive cocci from the oral mucosa of some patients.[13] Theoretically such organisms would not be affected by prophylactic treatment with penicillin and could cause bacterial endocarditis. There are isolated reports wherein bacterial endocarditis due to penicillin-resistant streptococci is described,[14] but currently it appears that the risk of such an eventuality is small. If the incidence of endocarditis due to such penicillin-resistant organisms increases, additional studies incorporating antibacterial agents other than penicillin for preoperative prophylaxis would appear to be indicated.

The results of our investigations to date should not be interpreted as indicating that we thereby advocate the abandonment of other forms of penicillin for prophylaxis before oral surgery. Other forms of penicillin given on differing schedules by various investigators have been effective and in fact have constituted the criteria by means of which we have assessed the results of our investigations. It does appear logical to conclude that when individual requirements are best satisfied by oral rather than parenteral medication and by a shorter duration of preoperative therapy, phenoxymethyl penicillin is employable. This conclusion appears to be reasonable, since phenoxymethyl penicillin has been as effective in decreasing the incidence of bacterial invasion of the blood after oral surgery as have alternate regimens. It can be argued that parenteral administration of penicillin preoperatively may produce more reliable blood levels, but this is countered by the fact that administration of penicillin parenterally is more likely to incite the occurrence of untoward reactions. No anaphylactic or other untoward reaction to phenoxymethyl penicillin has occurred among the patients in our studies to date. One might also conclude that since use of orally administered penicillin has been successful in eradicating subacute bacterial endocarditis due to Streptococcus mitis,[15] successful prophylaxis of the infection with the use of the same drug may be expected. In any event, it is well to recall that administration of an antibiotic before an oral surgical procedure is not a panacea; prior prophylactic treatment should not forestall diligent investigation if symptoms and signs of bacterial endocarditis develop postoperatively.

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Notice of Public Hearing
Minnesota State Board of Medical Examiners

"Notice is hereby given, pursuant to the provisions of Minnesota Statutes, 1961, S 15.0412, that the Minnesota State Board of Medical Examiners will hold a public hearing on Saturday, February 13, 1965, at 10 o'clock, A.M., in the auditorium of the State Office Building, Saint Paul, Minnesota, on the adoption of proposed substantive rules and regulations pertaining to professional corporations and to the practice of medicine and surgery, osteopathy, massage, physical therapy and midwifery, and of procedural rules and regulations pertaining to the hearing of contested cases before the Minnesota State Board of Medical Examiners.

Copies of the proposed procedural and substantive rules and regulations are available from the Secretary of the Minnesota State Board of Medical Examiners, 230 Lowry Medical Arts Building, Saint Paul, Minnesota, 55102.

Interested persons are invited to attend and submit data or views orally or in writing.

Dated at Saint Paul, Minnesota, this 23rd day of November, 1964.

By Order of the Minnesota Board of Medical Examiners
J. P. Medelman M.D.
Secretary-Treasurer"

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BRIEF SUMMARY

'SOMA' COMPOUND; 'SOMA' COMPOUND plus CODEINE: carisoprodol, acetophenetidin, caffeine, codeine phosphate. *Warning: Codeine may be habit-forming.* **Indications:** 'Soma' Compound and 'Soma' Compound with Codeine are indicated for relief of pain and stiffness in traumatic, rheumatic and other similar conditions. **Contraindications:** Allergic or idiosyncratic reactions to carisoprodol or codeine. **Precautions:** *Acetophenetidin*—May damage the kidneys when used in large amounts or for long periods. *Codeine*—Should be used with caution in addiction-prone individuals. *Carisoprodol*—Like other central nervous system depressants, should be used with caution in patients with known propensity for taking excessive quantities of drugs and in patients with known sensitivity to compounds of similar chemical structure, e.g., meprobamate. **Side effects:** *Codeine*—Nausea, vomiting, constipation, and miosis. *Carisoprodol*—The only side effect reported with any frequency is drowsiness, usually on higher than recommended doses. One instance each of pancytopenia and leukopenia occurring when carisoprodol was administered with other drugs has been reported as has an instance of fixed drug eruption with carisoprodol and subsequent cross-reaction to meprobamate. Rare allergic reactions, usually mild, have included one case each of anaphylactoid reaction with mild shock and angioneurotic edema with respiratory difficulty, both reversed with appropriate therapy. Other rarely observed reactions have included dizziness, ataxia, agitation, increase in eosinophil count, and gastrointestinal symptoms. Massive overdosage may produce coma and/or mild shock and respiratory depression. **Dosage:** 'Soma' Compound and 'Soma' Compound with Codeine, one or two tablets three times daily and at bedtime. **Supplied:** 'Soma' Compound, orange tablets, each containing carisoprodol 200 mg., acetophenetidin 160 mg., and caffeine 32 mg. 'Soma' Compound with Codeine, white, lozenge-shaped tablets, each containing carisoprodol 200 mg., acetophenetidin 160 mg., caffeine 32 mg., and codeine phosphate 16 mg. Narcotic order form required. *Before prescribing, consult package circular*

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Grand Rounds

Hypopituitarism

Introduction

To speak of pituitary insufficiency is to consider insufficiency of the target glands stimulated by the pituitary.

Since the early part of this century, much has been learned regarding hypopituitarism. Glinski in 1913, Simmonds in 1914, Sheehan and associates in 1937, and many other investigators have contributed much to the present knowledge of hypopituitarism.

The Pituitary Gland

The pituitary is a small gland with a normal dimension of about 10 × 13 × 6 mm. The average weight of the adult pituitary is 0.6 grams. It lies within a bony cavity, the sella turcica, in the spheroid bone at the base of the skull. Superiorly, it is separated from the cranial cavity by a tough reflection of the dura mater, the diaphragma sella, through which the pituitary stalk and attendant blood vessels reach the main body of the gland.

The gland receives a double blood supply. The internal carotid arteries supply the superior hypophyseal and inferior hypophyseal arteries which supply the anterior and posterior lobes, respectively. There is also an important pituitary portal system that supplies the whole gland. Venous blood from both lobes drains into the cavernous sinus. The anterior lobe is highly vascular, which may explain its vulnerability to ischemia.

The nerve supply to the anterior lobe is derived from the carotid plexus and appears to have a vasomotor function. A few neural fibers traversing from the posterior to the anterior lobe have been described, although their significance is not understood.

It should be noted that the pituitary is in close anatomical relation to important structures such as optic chiasm, carotid arteries, the third ventricle, the mammillary body, the cavernous sinus and the subarachnoidal space. This may explain the involvement of pituitary functions

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*Presented as a Medical Grand Rounds at Mt. Sinai Hospital, Minneapolis, September 22, 1964.

Continued

through anatomical contiguity. An example is aneurysm involving the sella turcica, a case of which was reported by Fine and associates in 1963 resulting in hypopituitarism.

The gland has a double origin. The adenohypophysis develops from the primitive mouth (stomadeaum, Rathke's pouch). The neuro-hypophysis arises from the downgrowth of the diencephalon. For this reason, their structure and function are quite distinct.

DIVISION OF PITUITARY GLAND

Adenohypophysis	Lobus Glandularis	Pars Distalis Pars Tuberalis	Anterior Lobe
		Pars Intermedia	Posterior Lobe
Neurohypophysis	Lobus Nervosus (Neural Lobe)	Procesus Infundibuli	
	Infundibulum (Neural Stalk)	Pediculus Infundibularis (Stem) Bulbus Infundibularis (Bulb) Labrum Infundibularis (Rim) or Median Eminence of the Tuber Cinereum	

Fig. 1 — Terminology Recommended by the International Commission on Anatomical Nomenclature.

Neurohypophysis

Origin: Diencephalon.

1. Nonmedullated nerve fibers — from hypothalamus.

Supraoptic Nuclei)
Paraventricular Nuclei) → Supraoptic-Paraventricular Tract → Pituitary Stalk
CNS
↓
Nervous Control

2. Neuroglia — contains granules of nonsecretory materials.

Hormones:

A. ADH (Both isolated and identified by Du Vigneaud as octapeptides.)

B. Oxytocin (Can be synthesized.)

ADH — control urine secretion.

Oxytoxin: A. Definite role in ejection of milk (probable stimulation of anterior pituitary to produce lactogenic or galactopoietic factors).

B. Probable physiological role in parturition in hastening labor by stimulating action on the uterine muscles.

Adenohypophysis

Origin: Stomadeaum, Rathke's Pouch.

Few nerve fibers but evidence of partial control by CNS.

Cells:

1. Chromophobes
↑ ↓
2. Chromaphils

A. Acidophils) a. Growth hormone — isolated, purified
) b. Probably lactogenic hormone

B. Basophils

   a. Oval or round cells $\xrightarrow{\text{probably}}$ gonadotrophins
   b. Angular or polyhedral $\xrightarrow{\text{probably}}$ thyrotrophic
   c. Lightly granulated → corticotrophin
3. Amphophiles
4. Hypertrophic Amphophiles

Hormones: Isolated in pure or almost pure forms

1. STH → Growth
2. ACTH & MSH → Adrenal cortex and melanin metabolism
3. TSH → Thyroid
4. FSH → Ovarian Follicle
5. ICSH or LH → Corpus Luteum (ovary) or Leydig Cells (testis)
6. Prolactin or lactogenic → Breast
   Probably identical to luteotrophin → Corpus luteum in non-pregnant (animals)

General Endocrine Principles

A general concept to explain the relationship of pituitary trophic hormones and the target endocrine glands (thyroid adrenal, gonads) has been proposed.

Effect on Target Glands of Variations in Quantities of Trophic Hormones Secreted

1. *Hypotrophism.*

With cessation of production of a trophic hormone, there is a pronounced atrophy of the respective target gland, with an associated decreased rate of manufacture and release of its hormone into the circulation.

2. *Hypertrophism.*

Hypersecretion of the trophic hormones leads to hypertrophy and hyperplasia of the target gland, with increased rate of manufacture and transfer of the target gland hormone into the blood stream. There may be an increased or decreased concentration of hormone within the gland.

Effect on Target Glands of Administration of Pituitary Hormone

After the administration of a pituitary trophic hormone, there is increased secretory activity of the target gland, and when the stimulus is intense and prolonged, hypertrophy and hyperplasia of the cell results, with increased rate of manufacture of hormone.

Effect on Pituitary of Variations in Quantities of Hormones Produced by Target Glands

1. *Hyposecretion.*

When the amount of hormone produced by the target gland is distinctly less than is required by the body, there is an increased elaboration of the trophic hormone, leading to hyperplasia and hypertrophy of the target gland.

2. *Hypersecretion.*

Generally an increased production of the respective trophic hormone is

Continued

found when there is excessive secretion by the target gland, the latter resulting from the former.

Effect of Target Gland Hormones on Release of Pituitary Hormone

The administration of a target gland hormone inhibits the production of the corresponding trophic hormone, with variable effects on the other trophic hormones.

Variations in Response of Body Cells to Different Hormones

Although all of the glandular hormones circulate in the blood stream and all of the cells of the body are exposed to them, the responses are influenced by genetic, environmental and other factors affecting the target cells.

Effect of Concentration of Various Body Constituents on Release of Hormones

The mechanism by which a gland is informed of the needs for its products varies, but the concentration in the blood of a specific substance often appears to be the chief determinant.

Possible Effects of Pituitary Insufficiencies

Varying symptomatology is brought about by general or selective deficiency of the pituitary hormones, depending upon the degree of involvement of the target glands.

These result from mild deficiencies due to disease states or to total therapeutic surgical removal (hypophysectomy) for various indications.

Neurohypophysis — Diabetes insipidus.
Adenohypophysis (Extreme insufficiencies)
A. Growth (young — growth ceases (dwarfism))
( ) Studies in animals
(adult — no skeletal changes)
B. Thyroid — atrophy — myxedema in 1-6 months.
C. Adrenal Cortex — atrophy — signs of insufficiency within 2-3 days.
D. Gonads — Before puberty — infantilism.
After puberty — atrophy of gonads.
  a. Male — Abolition of spermatogenesis ⟶ sterility.
  b. Female — Abolition of ovulation and menstrual cycle ⟶ sterility.
  c. Loss of axillary and pubic hair.
  d. Vaginal smear — postmenopausal in one week and atrophic within 2-4 weeks.
  e. Urinary gonadotrophin output ceases in 2-8 weeks.
  f. Absence of menopausal symptoms.
E. Increased sensitivity to insulin.
F. Mild and variable diabetes insipidus.

Simmonds' Disease

This disease is due to destruction or atrophy of the anterior pituitary gland due to any cause. If panhypopituitarism appears following postpartum hemorrhage, it is termed Sheehan's syndrome.

Clinical features are variable, depending upon which target organ and trophic hormone output is most severely affected. Usually gonad and thyroid deficiency findings are most striking.

This condition must be differentiated from anorexia nervosa, myxedema, and Addison's disease, among others. Differentiation of this disease from anorexia nervosa can be difficult. Both conditions may have psychic factors, although in anorexia nervosa there is usually a history of a more specific emotional stress. Anorexia nervosa is more common in the younger age group. Anorexia nervosa patients are more alert and active and can withstand stress. Failure to respond to hormonal replacement treatment is an indication that the pituitary is not insufficient.

Sheehan's Syndrome

It has been clearly demonstrated that interruption of the anterior pituitary blood supply is the pathology underlying this condition. Sheehan and Whitehead (1963) studied the relation of post-partum hypopituitarism to the neurohypophysis. In their series, they had 43 early cases (patients died from six hours to 35 days post partum) and 33 late cases (patients survived 2-50 years with evidence of hypopituitarism). In the 43 early cases, 25 had more than 95% destruction of the anterior pituitary with vascular lesions in the neural stalk in 14 cases; five cases had minor lesions in the posterior lobe. This suggests that the posterior lobe is less vulnerable to ischemia. Out of 33 late cases, 18 had less than 5 mm. of surviving anterior lobe tissue. Only one had a normal pituitary. Among eight cases with anterior lobe remnants of a 10-40 mm., only one had a normal posterior lobe. Two cases with more than 40 mm. of surviving anterior lobe had no lesion in the posterior lobe. In all cases, the pituitary stalk remained normal and diabetes insipidus was absent.

There are 17 cases reported in literature of Sheehan's syndrome with diabetes insipidus (Evans, 1960). Goth reported a case in 1963. All of these cases were reviewed by Sheehan and Whitehead and some were considered to be doubtful.

Pituitary Dwarfism (Lorain-Levi Type)

Pituitary insufficiency in childhood causes dwarfism. This may or may not be produced by a tumor. If caused by a tumor, it is most likely to be a craniopharyngioma. Suprasellar cyst and Hand-Schuller-Christian disease may cause hypopituitarism.

Examination usually reveals a small child with normal proportions. The only clinical manifestation may be wrinkling of the skin and growth retardation. Mentality is unaffected. The involvement is usually not limited to growth hormone.

Recently human growth hormone (HGH) has become available for experimental use. Only human and monkey HGH produces significant metabolic effects in man.

Trafford and associates used HGH in four patients with pituitary dwarfism. In all four the rate of growth more than doubled with nine to fourteen months' treatment. Mockenberg used HGH in six infants who were severely malnourished. There was a marked gain in weight, positive Na, K, and P balance within 40 days, reverting to pretreatment levels soon after cessation of hormonal stimulation.

Continued

Methods for Diagnosis of Hypopituitarism

There are promising results in the determination of HGH levels; however, these are not fully standardized or clinically available. If perfected, the HGH level will be the best confirmatory test for the diagnosis of hypopituitarism.

Thyroid function can be evaluated by determination of serum protein-bound iodine, thyroid I^{131} uptake, and thyrotropin stimulation.

Evaluation of adrenal cortical function may be made by plasma and urine 17-hydroxycorticoid measurement and ACTH stimulation. Metapirone (SU-4885) is an adrenal cortical blocking agent which selectively inhibits the enzyme 11 beta hydroxylase necessary for the formation of cortisol. With the blockade of cortisol synthesis, desoxycortisol (Cpd S) is produced in excess, but has little inhibitory effect on pituitary ACTH release. With a normal pituitary, the decrease in plasma cortisol level results in an increased output of ACTH and increased levels of Cpd S in blood and urine, which can be measured as Cpd S or as 17-ketogenic or 17-hydroxycorticosteroids. Metapirone thus results in a test of pituitary ability to put out ACTH, if the adrenal cortex is capable of functioning.

Evaluation of gonadotrophic function consists of bioassay of FSH and LH or ICSH in urine. Estrogen effect can be studied by cytological evaluation of vaginal smears. Pyknotic nuclei and pink cornified cells are evidence of normal estrogen stimulation.

As for the evaluation of function of the neurohypophysis and the diagnosis of diabetes insipidus, the effect of hypertonic saline on urinary output can be studied as described by Hickey and Hare, although the vasopressin (Pitressin) test may be sufficient. The Hickey-Hare test must be used cautiously in older patients, particularly if heart disease is present.

Treatment

All pituitary hormones are protein in nature and must be administered parenterally. Oral administration results in destruction of the hormone by the gastric acid. There are six hormones elaborated by the anterior pituitary, but only ACTH and TSH are commercially available, and are largely used as diagnostic agents.

Because of the difficulty of continuous anterior pituitary hormone replacement, therapy must be aimed at end-organ deficiencies. Cortisol or cortisone is given to replace deficient adrenal cortical output. Mineral corticoids are not necessary in pituitary insufficiency, since aldosterone continues to be produced. Sex hormones (testosterone) may be used in both males and females for its tissue building (anabolic) effect and estrogen in females for its anabolic effect, effect on secondary sex characteristics, and prevention of osteoporosis. Posterior pituitary hormones, oxytocin and vasopressin have been synthesized. The main indications for oxytocin are obstetrical. Vasopressin is used in the treatment of diabetes insipidus. Thyroid hormone is given to treat the thyroid insufficiency. Chlorothiazide diuretics may be symptomatically beneficial in diabetes insipidus.

Case Report

A 41-year-old married white female chemist was admitted to Mount Sinai Hospital August 13, 1964, with chief complaints of fatigue, nervousness and insomnia present and progressively increasing over a 2-3 year period. The patient's weight had gone down from 103 pounds in 1953 to 82 pounds on admission. She had noted swelling of her ankles during the hot summer months. She also complained of irregular heart beat. She had had no menstrual periods for the past ten years following a post-partum hemorrhage after the delivery of her second child. There had been no loss of libido, and skin and hair had been normal.

In the past a diagnosis of anorexia nervosa had been made.

Physical examination was negative except for evidence of weight loss and nervousness. Axillary and pubic hair was present but sparse. Pelvic examination was negative except for dry vaginal mucosa with redness and friability.

Laboratory studies yielded the following results. Electrocardiogram showed no significant abnormality. X rays, including the skull, were within normal limits. Hemogram was normal. Serum electrolytes were normal. Serum protein-bound iodine was 6.3 mcg.%, and basal metabolism rate plus 6. Eosinophil count was 305 per cu. mm. Sedimentation rate was 5 mm/hr. VDRL was negative. Vaginal smear showed lack of estrogenic stimulation consistent with the menopausal period.

The twenty-four hour urinary follicular stimulating hormone excretion was less than six mouse units. Urine excretion of 17-ketogenic steroids was 6.2 mg. in 24 hours. An ACTH test (25 units in a 4-hour intravenous infusion) produced a two-fold increase in the plasma cortisol level. A metapirone test resulted in no increase in urinary 17-ketogenic steroid level.

A diagnosis of pituitary insufficiency, probably Sheehan's syndrome, was made and treatment instituted.

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Careless Observation

If the matter is one that can be settled by observation, make the observation yourself. Aristotle could have avoided the mistake of thinking women have fewer teeth than men by asking Mrs. Aristotle to keep her mouth open while he counted. He did not do so because he thought he knew. — Bertrand Russell

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If women's intuition is so good, how come they have to ask so many questions?
— Pipe Dreams

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Industrial Medicine

Employment of Diabetics

Joseph T. Beardwood, Jr., M.D.*
Abington, Pa.

In 1951 the Council of the American Diabetes Association appointed a Committee on Employment. Most of our patients were gainfully employed, and until it was called to our attention, we were not aware of the discrimination against employment of diabetics in certain areas and certain industries. It was felt that this Committee should attempt to promote the right attitude in regard to diabetics as employees. After consultation with industrial physicians, personnel directors and labor organizations, the Committee on Employment issued its first statement.[1] "It is the philosophy of the American Diabetes Association that controlled diabetics without complications are good employable risks. They should not be classed as vocationally handicapped, for they are capable of satisfactorily performing a full day's work, despite their diabetes, in most positions."

All our statements have emphasized that we are referring to diabetics who keep their disease controlled and who visit their physicians regularly. We pointed out that diabetics fall into two groups: first, those who are controlled on diet alone and present no problem whatsoever, and second, those who require insulin in addition to diet for control. The latter, we felt, were able to do any work for which they were mentally and physically qualified, except that they should avoid positions where an insulin reaction might imperil their health or the safety of other workers. Our statement attempted to set up standards for satisfactory control.

The Committee then canvassed the Industrial Hygiene Association, members of which represent large industries with adequate Medical Departments. The survey showed that, by and large, this group employed diabetics and permitted them to participate in all fringe benefits.[2] Coincidentally with the life of this Committee there has been a great increase in industrial medical departments which play an ever larger part in determining the employment policies and participate more and more in the general health problems of employees.

During this time many papers have been written on the employment of diabetics, mostly from industries with adequate medical departments which have been able to compare employment records of diabetics and nondiabetics. Two of the most comprehensive papers on the diabetic as an employable risk are those by Leo Wade[3] and by Sidney Pell and C. A. D'Alonzo,[4] which show that the experience with diabetics has been as good as with nondiabetics. In many cases the self-disciplined, well-controlled diabetic has proven to be a better risk than his nondiabetic brother. These two papers are very well documented and have been published through companies whose medical departments are well organized. As a result of these studies the A.D.A. has published a pamphlet entitled "Diabetics are Good Employees," a copy of which can be obtained from the A.D.A. headquarters.

In spite of sufficient evidence that controlled, conscientious diabetics are quite satisfactory employees, there still seems to be a certain amount of discrimination against their employment, and prejudice on the part of personnel directors, who at times guide

Continued

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*Chairman, Committee on Employment, American Diabetes Association.

the employment policies. Occasionally there is an arbitrary attitude on the part of the medical director.

In most instances diabetics participate satisfactorily in fringe benefits, but early retirement can be a problem in certain of the large industries where employees may be retired on a pension or other retirement benefits at the age of sixty. There has been some trend on the part of industry to retire diabetics early, which, unfortunately, has been abetted by many physicians willing to state that diabetes is a reason for early retirement, regardless of the presence or absence of any complications. This has made many industries hesitate to employ diabetics for long-term positions and represents a very adverse attitude on the part of some members of the medical profession.

Much can be done at the local level throughout this country, possibly more than at the national level, to persuade industry to employ diabetics. Progress has been made through various affiliates of the American Diabetes Association, regional organizations composed of physicians and laymen, to persuade local industries and often local branches of national companies, that diabetics are very good risks; however, much remains to be done. The individual physician, with his standing in the community and his contact with business employers, can do much to prevent diabetics from being classified with epileptics and other handicapped individuals.

There is a great deal of activity on the part of the President's Committee for the Employment of the Handicapped, of which the author of this paper is a member. Their interest has been devoted to truly handicapped individuals, and they have been, to some extent, successful in helping to obtain employment for these people. However, our philosophy is that the well-controlled diabetic is not a handicapped individual, but can, if given a chance, prove his ability to hold any job for which he is mentally and physically capable.

The United States Civil Commission has somewhat over one hundred positions for which they will accept a controlled diabetic. As the largest employer in the country, their experience has been quite satisfactory over some ten years.

While some progress has been made, much more remains to be achieved. A most pathetic situation is that of a well-educated, young diabetic coming out of college, seeking a job for which he is fully qualified, only to be told by the first interviewer that because of his diabetes he is not acceptable. Psychologically, this is a severe blow and has given many of these well educated young people a complex about their future.

The attitude of our Committee is that diabetics should not expect favors because they are diabetic, but, on the other hand, should be given a chance to demonstrate their ability to hold any given job. We have issued another pamphlet, "Guide Posts to Diabetics Seeking Employment," emphasizing this philosophy.

It is our hope that the medical profession at large will take more interest in this situation which often prevents a very worthy group of people from carrying their full measure of responsibility.

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One way to get along in life is to co-operate with the inevitable.—Herbert Prochnow

Abstracts, Briefs and Commentaries

HEMODYNAMIC STUDIES AFTER MITRAL COMMISSUROTOMY

The authors reviewed 33 patients selected for study because of pure or predominant rheumatic mitral stenosis. Patients were evaluated pre and postoperatively by left heart catheterization data, phonocardiograms, and auscultation. There were 20 females and 13 males. Average age was 36 years but the ages ranged from 13 to 58 years. Mitral commissurotomy was generally performed by the transventricular dilatation of the valve in those cases where digital fracture was not deemed necessary. In three cases a malleable knife was used in conjunction with digital or mechanical dilatation. The patients were classified into three types: type 1 had fusions of the mitral commissures but both leaflets of the valve retained normal mobility, type 2 had fusion of the commissures but the anterior leaflet was immobile although the posterior leaflet was rigid and fixed, and type 3 had fusion of the commissures but both leaflets were completely immobile. Twenty patients by hemodynamic catheterization studies had a satisfactory operation but 13 patients did not. The authors then reviewed the results.

Adequate commissurotomy was effected in 15 of 20 female patients but only five of 13 male patients. The best results were obtained in the age group under 35 years, although satisfactory results were also obtained in the older ages. The most important preoperative auscultory finding was the loud opening snap. Ten of 12 patients with loud opening snap had a satisfactory commissurotomy. Only eight of the 18 patients in whom the opening snap was inconspicuous had a satisfactory mitral commissurotomy. The presence or degree of generalized cardiac enlargement did not bear relationship to the operative result. Radiographic evidence of calcification in the region of the mitral valve was found to be an important factor. It was absent in 22 patients and of these satisfactory commissurotomies were achieved in 15. More than half of the patients in whom calcification was present had unsatisfactory results. The preoperative severity of the stenotic lesion by cardiac catheterization did not bear any relationship to the final result.

An extremely significant observation was that the calcification was absent in all patients with a type 1 valve. Calcification was present in all

Continued

patients with a completely immobile type 3 valve. Calcification was visible about 50% of the time in type 2 valve.

The authors conclude that open-heart surgery might be necessary in patients in whom a type 3 valve is suspected. I would agree that if there is clinical evidence that a rigid valve is present, the patient should best be approached by the closed method but with the extracorporeal unit on stand-by, such that valvular prosthesis could be inserted to avoid a second operation. The clinical suspicion that an immobile valve might be present would be the result of the auscultatory findings plus the radiologic evidence of calcium in the mitral area.

Jerome T. Grismer, M.D.
Minneapolis, Minn.

Morrow, A. G., du Plessis, L. A., Wilcox, B. R.: Surg 54:463, 1963

PULMONARY EMBOLISM IN CHILDREN

Pulmonary embolism is generally believed to be rare in childhood, but there were 25 cases in 2000 autopsies on live-born children in the Sheffield Children's Hospital in the last ten years. Five of these children were newborn and the others were 13 weeks to seven years old.

In the neonatal group the primary site of venous thrombosis was in the cerebral veins in two, the venous hepatic channels in two and the inferior vena cava and mesenteric and renal veins in one. In the older children cerebral venous sinus thrombosis had occurred in nine cases, thrombosis of nasopharyngeal veins in five, of the lower abdominal and pelvic veins in four and the inferior vena cava and renal veins in two. In three cases the site of primary thrombosis was not discovered.

From the clinical data it was clear that the symptoms of pulmonary embolism are much like those of acute respiratory infection. A usual clinical diagnosis is acute pneumonia. There may, however, be sudden death in a sick child. In children pulmonary embolism is always a complication of other diseases; the commonest precipitating lesions are cerebral hemorrhage or thrombosis, septic processes in the lower abdomen, cachexia and severe nasopharyngeal infection.

Courtesy of World-Wide Abstracts

Emery, J.: Arch Dis Child 37:196,591

SCLEROSING CHOLANGITIS

The coexistence of sclerosing cholangitis, chronic fibrous thyroiditis (Riedel's struma), and fibrous retroperitonitis suggests a possible etiological relationship. The usual clinical picture is that of obstructive jaundice suggesting common-duct stone or carcinoma of the head of the pancreas. The diagnosis can be definitely established only at operation when classic findings of diffuse irregular thickening of the wall of the common bile duct and almost complete obliteration of its lumen are encountered. This paper reports two cases of sclerosing cholangitis intimately related to the diffuse sclerosing process, fibrous retroperitonitis. Isolated involvement of the common bile duct and Riedel's struma may be atypical or abortive forms of more generalized disease.

Courtesy of References and Reviews
Journal of the American Medical Association

Bartholomew, L., Cain, J., Woolner, L., Utz, D., and Ferris, D.: New Engl J Med 269:8, 1963

GASTROENTERIC CUTANEOUS FISTULA-TRACT OCCLUSION FOR TREATMENT

The author has revived the method of controlling chronic fistulas of the interabdominal organs by the simple expedient of closing the fistula with some method of external packing: an old method, first tried as early as 1827. He felt that it was a method that was applicable in certain instances. In the four cases in which this method was utilized, the author points out that the patients undoubtedly would have died because of the severe complications of the fistula, fluid loss, hemorrhage, poor nutritional status secondary to a prolonged illness and continued inability to control the fluid losses. (Of the four patients treated, three had spontaneous healing of their fistulas.)

Tract occlusion is advocated only in the management of chronic fistulas after a firm fibrous tract has developed. Certain requirements should be met before tract occlusion is utilized: (1) it must be determined that the gastrointestinal tract is patent distal to the point of the fistula as obstruction contraindicates this method, (2) there should be no active infection in the area of the fistula, (3) roentgenologic studies should demonstrate that the fistula's tract is a single one without evidence of lateral pockets. The means of occluding the fistula are not as important as doing the procedure.

Comment: This is an excellent article to be read and remembered.

Jerome T. Grismer, M.D.
Minneapolis, Minnesota

Jordan, G. L., Jr.: AMA Arch Surg 88:540, 1964.

RENAL ARTERIAL LESIONS

In 72% of a group of hypertensive patients with renal arterial disease, urographic signs of disparity in renal length or dye concentration, or both, reflected the presence of stenotic lesions and served as indications for renal arteriography. Urographic films were satisfactory for these measurements in 128 of 139 patients, and 92 were found to have abnormalities. Similar urographic signs were found in only 8% of 127 patients with essential hypertension. In the absence of urographic abnormalities, some clinical features were suggestive of renal arterial disease and served as indications for arteriography. These were malignant hypertension, particularly that developing abruptly in a recently normotensive individual, hypertension in patients less than 35 years of age, sudden acceleration of vascular disease, abrupt onset of hypertension after the age of 35, epigastric bruits, and signs of generalized atherosclerosis.

Courtesy of References and Reviews
Journal of the American Medical Association

Wilson, L.: Arch Intern Med 112:270 Aug. 1963

IDIOPATHIC HEMOCHROMATOSIS

Idiopathic hemochromatosis appears to be an acquired rather than a genetic disease, a variant of "alcoholic" or nutritional cirrhosis, or of conditions leading to cirrhosis. It has been assumed that the diet of afflicted persons contains only normal amounts of iron. There is, however, a known association wtih the use of alcohol, and most cases have been reported from wine-consuming countries. There is no mucosal block to iron absorption, so that the iron of wine, in the amounts ingested in countries where hemochromatosis is common, is sufficient to account for

Continued

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the disease. The source of metals in wine is chiefly from the equipment used in preparation. Other sources of dietary iron may similarly exist, and should be sought in patients with the disease, such as nonprescription medicines containing iron, iron cooking utensils, and "home-made" alcohols. Factors of diet, pancreatic disease, and hematologic disease may also contribute to excess iron absorption and tissue deposition.

Courtesy of References and Reviews
Journal of the American Medical Association

MacDonald, R.: Arch Intern Med 112:184 Aug. 1963

HYDROCORTISONE IN SEVERE INFECTIONS

A multihospital double-blind study of the role of corticosteroids in 194 patients with severe infections failed to produce evidence of any appreciable benefit in such cases, and whatever slight indication there was of an adverse effect was not considered statistically significant. The infections were of varied type and etiology, no one of which showed any evidence of differing from the others insofar as the action of hydrocortisone was concerned. The authors add, however, that most of the groups were so small that any confident conclusion could be based only on the over-all total. Perhaps one of the more valuable things to emerge from the study was the demonstration that multihospital groups of this kind can carry on controlled double-blind studies, even in life-threatening acute infections.

The patients studied ranged in age from sixteen to seventy-five years (children under sixteen were included in one institution, but are not included in the statistical analysis). The study group included 85 patients with meningitis of various types; pneumonia, tuberculosis, and various staphylococcal and gram-negative infections accounted for the rest.

Kits had been prepared containing six vials, each carrying 100 mg. of (a) hydrocortisone or (b) placebo, plus a sufficient number of 25 mg. tablets for tapering-off oral therapy. Patients admitted with apparently life-threatening infections were given all indicated antibiotic and supportive therapy, but no corticosteroids. Instead, the unidentified kits were used as follows: The contents of three vials were given intravenously the first day, and two and one half vials on the second over six to eight hours. The last four days treatment was oral unless the patient was unable to swallow, in which case special arrangements had been made to continue intravenous therapy. Starting on the third day, the patient got 200 mg. by mouth; 150 mg. on the fourth day; 100 the fifth; and 50 the last day. Therapy was started when antibacterial agents were first given, or at the time that a major change in antibacterial therapy occurred, and not simply when everything else failed. The hydrocortisone and placebo groups were of approximately equal size. The clinicians in charge, but none of their staff, knew which kit contained the corticosteroid and which contained the placebo.

The statistical analyses are extensively tabulated and graphed. In the sixteen to twenty-five year age group the only fatalities appeared in the patients given the hydrocortisone. This was also true in the twenty-six to thirty-five year group. In the thirty-six to forty-five year age group, fatalities are represented as about equal between the patients given the hydrocortisone and those given the placebo. Fatalities rose with age re-

Continued

gardless of treatment; in the group over fifty-six years old, the advantage appears to be with the placebo group, but the difference is not regarded by the authors as statistically significant.

Courtesy of Medical Abstract Service
Berwyn, Illinois

Cass, Edward H.: J Amer Med Ass 183:462, 1963

CONSTRICTIVE PERICARDITIS

Of 21 patients operated on for constrictive pericarditis, 4 died postoperatively but 13 are known to be working full time.

The condition may be caused by tuberculosis or viral infection. In the latter case it is called nonspecific. The Coxsackie B_5 virus has sometimes been found in the feces of patients.

In the tuberculous group the average duration of illness before operation is three years, compared with ten months in the viral group. The tuberculous cases are sparsely scattered over many years whereas the nonspecific cases appear in epidemic crops.

In the tuberculous cases the pericardium is greatly thickened, to about 1 cm., with areas of calcification or necrosis; in the virus group it is smooth and less thickened. The onset is gradual in the tuberculous cases and acute in the virus group. The tuberculous cases often show a tendency to invade the myocardium, which is rare in the virus group.

Early operation is essential in the viral group. Tuberculous pericarditis does not respond well to pericardiectomy during the acute phase. If it is diagnosed in this phase, operation should be preceded by several months of chemotherapy. Both ventricles must be completely freed of the constrictive pericardium for a good functional result. A left thoracotomy gives the best exposure for this purpose.

Courtesy of World-Wide Abstracts

Robertson, R., and Arnold, C.: Circulation 26 4 (1):525

FAMILIAL INCIDENCE OF ULCERATIVE COLITIS

The family occurrences of ulcerative colitis, regional enteritis, and ileocolitis were investigated among 1,339 patients with these diseases. Positive evidence was obtained in 66 of 1,084 patients with ulcerative colitis; among the 89 family members 75 had ulcerative colitis, 13 had regional enteritis, and one had ileocolitis. Positive evidence was obtained in 20 of 185 patients with regional enteritis; among the 22 family members 12 had regional enteritis, nine had ulcerative colitis, and one had ileocolitis. Positive evidence was obtained in five of 70 patients with ileocolitis; the five family members included four with ulcerative colitis and one with regional enteritis. In all, 91 of 1,339 patients produced information for the occurrence of similar diseases among 114 additional family members. Ulcerative colitis was more common than regional enteritis in the families with ulcerative colitis and vice versa for regional enteritis. However, the family intermingling of these diseases suggests an etiologic interrelationship.

Courtesy of References and Reviews
Journal of the American Medical Association

Kirsner, J., Spencer, J.: Ann Intern Med 59:133, 1963

PERFORATION OF THE GALLBLADDER

Two hundred and eighteen patients underwent surgery by the authors for acute cholecystitis. In this series 21 patients (10.4%) had acute perforations of the gallbladder. Twelve of the cases of perforation were into the free abdomen and in nine cases the perforation was with formation of a pericholecystic abscess. The sexes were equally divided and the ages varied from 48 to 89 years. Four cases of the 21 had jaundice, chemically as well as clinically. Sixteen gave a history of more than one previous attack.

The gallbladder of three patients perforated on the second day, four on the third day, five on the fourth day, and three on the fifth and sixth days. The remaining patients had rupture of the gallbladder on later days but all perforated within ten days. In eight patients a preoperative diagnosis was made of a perforated gallbladder.

The types of operations ranged from cholecystectomy in twelve cases (four deaths), cholecystectomy and exploration of the common bile duct, and cholecystostomy. In one case only drainage of the abdominal cavity was carried out, and the patient survived.

Five deaths occurred in this series, three of these from peritonitis, one of pulmonary embolism, and one with uremia.

It was the authors' opinion that the signs and symptoms of perforation of the gallbladder are not distinct and consequently delay in diagnosis and subsequent delay in operative intervention are factors contributing to a high mortality rate. They felt that organ perforation was more common in individuals over the age of 60 years; also, that conservative treatment of acute cholecystitis could be hazardous because of the incidence of perforation prior to the tenth day. Although the operation depended on the status of the patient, the procedure varied from cholecystostomy to cholecystectomy and even exploration of the common bile duct. The authors indicated that cholecystectomy should be performed at the time of the first attack, as a vast majority of the patients with perforation of the gallbladder had antecedent histories of acute cholecystitis treated conservatively.

Jerome T. Grismer, M.D.
Minneapolis, Minn.

McEachern, C. G., Sullivan, R. E.: AMA Arch Surg 87:147, 1963

ROENTGEN DIAGNOSIS OF DIVERTICULITIS

A study of 100 cases of diverticula and 300 cases of diverticulitis of the colon permits the following statements: (1) Acute diverticulitis is characterized roentgenologically by palpable tenderness associated with extraluminal defects, edematous mucosa, obstruction to barium enema, fistulas, and sinus tracts. (2) The roentgen features of chronic diverticulitis are a saw-tooth appearance, extraluminal defects, and deformed diverticula. (3) The roentgenologic manifestations of both the acute and chronic stages may be seen in the same case. (4) Spot roentgenograms of the sigmoid in the left posterior oblique position are important in roentgenologic diagnosis.

Courtesy of References and Reviews
Journal of the American Medical Association

Olson, R., Hodgson, J., and Sauer, W.: Radiology 80:392, 1963.

BREAST CANCER

Dr. Crile has been interested in determining the value of less extensive operations for breast cancer, as compared with standard radical mastectomy. References are cited supporting the thesis that lesser procedures, i.e., simple mastectomy, are as effective, or more effective, as well as less productive of operative complications.

A five-year follow up is reported on 183 patients with breast cancer treated at the Cleveland Clinic Hospital. The study was designed so that half of the operable patients were treated by simple mastectomy and half by radical mastectomy. There was a slightly higher proportion of Stage 2 tumors in the group treated by radical mastectomy. Half of the group treated with radical mastectomy had a modification of the standard procedure in that the axillary dissection was performed with preservation of the pectoral muscles. Postoperative radiation was given to 44% of the group treated by radical surgery and to 42% of the group treated by simple mastectomy.

At five years 64% of the patients treated by simple mastectomy were alive, two of them with recurrence, while 58% of those treated by radical operations were alive, three with recurrence. The figures are selective in that 84% of the patients treated by simple procedures were classified in the clinical Stage 1 category, while 61% in the radically operated group were in Stage 1 classification. To be also considered, however, is the fact that Stage 2 patients treated by simple mastectomy were usually those with the most advanced disease. Even allowing for the increased proportion of Stage 1 patients in the group treated by simple procedures, there is still a 2% difference in survival rate favoring the lesser procedure.

Projection of survival curves showed no delayed tendency for results of radical mastectomy to become superior. Local recurrences were about the same in each group.

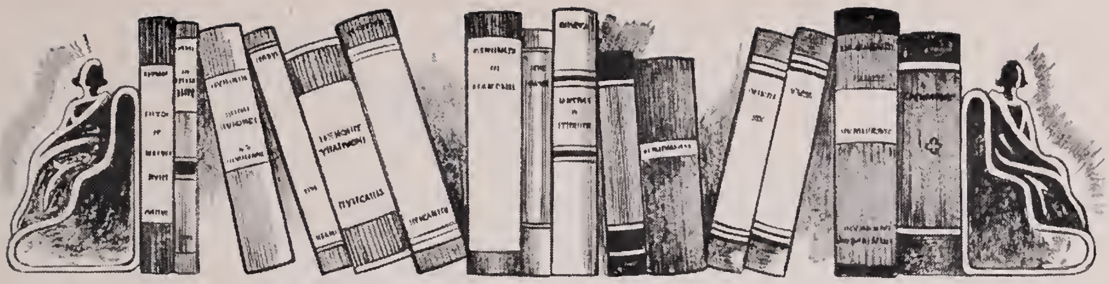
Six, or 46%, of 13 patients who had radical excision and proven involved nodes, are alive, but only four, or 31%, are free of disease. In the group treated by simple mastectomy, seven, or 58% of the 12 patients who had axillary dissections delayed until nodes became clinically involved, are alive without evidence of disease.

Dr. Crile believes his data suggest that a clinical Stage 1 patient is better treated by the lesser operative procedure. His hypothetical explanation is based on the theory that destruction of the regional lymph nodes, where lymphocytes become immunized against cancer, might diminish the immunological resistance of the host to implantation and growth of circulating cancer cells.

COMMENT: The data provided by Dr. Crile present an impressive case for conservatism in the surgical management of Stage 1 breast cancer. One is occasionally forced to wonder facetiously if the conflicting array of statistics and conclusions in a controversial field such as this doesn't imply a variability based on geographical circumstances. This would be an interesting subject for some local expressions of opinions from readers of Minnesota Medicine. What do you do?

Robert N. Hammerstrom, M.D.
Minneapolis, Minn.

Crile, G.: Results of Simplified Treatment of Breast Cancer. S G & O 118:517, 1964.



Book Reviews

Some books are to be tasted; others swallowed; and some few to be chewed and digested.—Bacon

YOUR WEIGHT AND HOW TO CONTROL IT — **Morris Fishbein, M.D., 1963 by Doubleday and Company, Inc., 206 pages.**

This book is for the layman, edited by Dr. Morris Fishbein, with twelve contributing authors. Although the text is somewhat superficial in its treatment of the various phases of obesity, it does give an overall picture of the problems involved in the causation, treatment and complications of the overweight person. Included in the material presented are the newer height and weight tables, developed by the Society of Actuaries and the Metropolitan Life Insurance Company, in 1959, and an appendix presenting diets of an exchange type for weight reduction. Answers are presented to many of the questions asked by the obese patient, or the parent of an obese child. This book is well worth reading by patients who are disturbed by their obesity and motivated to reduce weight, and will give them a better understanding of the problems involved. It will be of considerably less interest to the physician. Physicians, however, will find it useful as recommended reading for their patients, and for this reason would be well advised to read it first.

Alvin Schultz, M.D.
Mt. Sinai Hospital
Minneapolis, Minn.

BUSINESS MANAGEMENT OF A MEDICAL PRACTICE — **Bernard D. Hirsh, LL.B., C. V. Mosby Co., 5/11/64. 183 pp. $7.75**

The author, director of the law department of the American Medical Association, displays a considerable amount of insight into the business and legal aspects, as well as the practical considerations, of a medical practice.

Throughout the book, the emphasis is on the need for comprehensive written agreements between partners, physicians who share office space and expenses, an employer and associate, a hospital and medical specialist, and tenant and landlord.

Model contract forms are presented at the end of each chapter, as well as optional provisions to enable the tailoring of the agreement to the specific needs of the parties. As the author states, the purpose of the book is not to enable the physician to draft his own contract. It is intended to "help physicians to recognize the areas in which an understanding and agreement should be reached . . ." — with legal advice.

The chapters dealing with partnerships and the selling of a medical practice include discussions of the pertinent income tax issues. The sections dealing with gift and estate taxes and gifts to minors are especially informative.

The separate chapter devoted to the federal income tax is somewhat detailed and complex, and is not intended to be a resume of tax-saving devices. However, it does provide some useful and concise illustrations of important tax considerations.

The book should prove to be a worthwhile addition to the library of the physician, and it should have special appeal to the beginning practitioner.

H. S. Weiner
Field, Kuusisto & Froehlich
Certified Public Accountants
Minneapolis, Minnesota

COLLECTED PAPERS IN SURGERY FROM THE MAYO CLINIC AND THE MAYO FOUNDATION VOL 55 — **1964, W. B. Saunders Co. No price listed**

This book summarizes the surgical publications from the Mayo Clinic from December 1962 — November 1963. The longer articles have been abridged or abstracted, although numerous X rays, drawings, photographs, and photomicrographs have been included.

The data presented in these articles is of particular interest to the practicing surgeon as a reference source. He can then proceed in the handling of a given problem, not relying entirely on his own limited clinical experience but using as an adjunct the rich experience represented in these reports from this remarkable institution.

Harrison H. Farley, M.D.
Minneapolis, Minnesota

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Perinatal Mortality Study

Teratoma of the Liver in a Newborn*

The mother of the infant in this report was 20 years old; she was unwed and this was her second pregnancy. Her first child was completely normal. She had had no illness during the present pregnancy, and the only medication she received was oral iron, which brought her hemoglobin from 12.6 grams % to 14.2 grams %. Her prenatal course was otherwise normal, and her serologic test for syphilis was negative. She was Rh positive.

The Newborn Baby

She was admitted to the hospital at 35 weeks of gestation with the feet presenting. Upon delivery the female infant weighed 5 lbs. 2 oz. and measured 18 inches in length. The head circumference was 11⅝ inches and the chest circumference 12 inches. The abdomen was not measured.

Physical Findings

At birth the pediatrician noted that the infant's abdomen was distended, due to enormous enlargement of the liver and spleen, the liver extending all the way to the pelvis and the spleen half way to the pelvis. There was edema of the abdomen and minimal edema of the extremities. The infant had very little response and a weak, high-pitched cry. Rales were heard over the entire chest. The Moro reflex was absent.

Laboratory Studies

Laboratory tests done at birth revealed a cord hemoglobin of 14.5 grams %, bilirubin 1.4 mgm. % direct and 2.9 mgm. % indirect for a total of 4.3 mgm. % (Table 1). Both mother and infant were group O Rh positive. The cord Coombs test was negative. No reducing substances were found in the infant's urine and urinalysis was normal. A dye test for toxoplasmosis and a Kline test for syphilis were both negative on the infant's blood. A chest X ray was interpreted as follows: "A large mass occupies the major portion of the abdomen on the right side and displaces the stomach and small bowel to the left and posteriorly. The nature of the mass is not obvious, but it contains no calcification. It seems to have been present for some time, as the lower ribs on the right side are flared, and there is posterior bowing of the lower thoracic and lumbar spine."

Progress and Treatment

At six hours of age, the infant's bilirubin was 2.5 mgm. % direct and 7.0 mgm. % indirect for a total of 9.5 mgm. %. The pediatrician performed an exchange transfusion with 288 cc. of blood given and 317 cc. removed. Four cc. of calcium were given during the exchange transfusion.

The infant received constant oxygen in the incubator. At 12 hours of age, it was started on beta lactose feedings every four hours, and was also given aqueous penicillin 50,000 units every eight hours I.M. along with streptomycin 50 mgm. daily I.M.

When the infant was 20 hours old, its jaundice increased, and the

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*Ramsey County Perinatal Mortality Study Committee.

Continued

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pediatrician felt that the child was doing very poorly. The bilirubin was 1.0 mgm. % direct and 9.3 mgm. % indirect for a total of 10.3 mgm. %, (Table 1).

TABLE I

Teratoma of the Liver in a Newborn
Case Report and Comment
Ramsey County Perinatal Mortality Study Committee

Age of Infant	Bilirubin mgm. % Direct	Indirect	Total	Hb. gm. %
Birth — cord	1.4	2.9	4.3	14.5
6 hours	2.5	7.0	9.5	13.9
Exchange Transfusion at 10 hours				
Following Exchange Transfusion	1.0	1.8	2.8	
30 hours	1.0	11.0	12.0	15.3
20 hours	1.0	9.3	10.3	15.6

The pediatrician had ruled out Rh disease, ABO incompatibility, syphilis, toxins and drugs; toxoplasmosis was subsequently ruled out by a negative blood test. Sepsis was avoided by using antibiotics. The differential diagnosis included cytomegalic inclusion disease, hepatoma, congenital leukemia, and neoplasm of the liver.

The infant exhibited increasing respiratory distress and expired at 30 hours of age.

Post-mortem Findings

Autopsy of the infant read as follows:

Gross Pathology

The abdominal cavity is occupied by an *enlarged liver* which crowds all other abdominal viscera posteriorly and to the left. The inferior margin of the lobe of the liver is in the pelvis. The left lobe of the liver extends below the umbilicus. A large tumor mass occupies a great proportion of the right lobe of the liver. The liver weighs 510 grams. The capsule of the liver is intact. The left lobe of the liver is uninvolved by the mass. The mass is somewhat soft. On section these are hemorrhagic areas, and the mass seems fairly demarcated from the surrounding grossly normal liver which is compressed by the mass. The mass has a tan to pink color.

The *spleen* weighs 5 grams and has a normal size, shape and consistency.

The *kidneys* weigh approximately 5 grams apiece. On bisection the renal cortex is of the usual thickness. The cortical medullary border is distinct. The apices of the renal pyramids present yellow discoloration.

The *left lung* weighs 15 grams, the *right lung* 20 grams. Both lower lobes and a portion of each upper lobe present a compressed cyanotic appearance with a slightly increased consistency and absence of crepitance.

Microscopic Pathology

Microscopic sections of the *sternal marrow* show a nidus of endochondral bone formations. There is an increased portion of red cell progenitors consistent with the age of the patient. There are no abnormal cells noted.

Continued

Microscopic *sections of the lungs* reveal incomplete expansion of the lungs with broad areas in which neither the alveolar ducts nor the alveolar spaces are expanded. In these areas the alveolar walls lie in apposition. The septal capillaries are congested. Many of the alveolar spaces contain a pink hyaline to granular staining material. In some areas there is irregular expansion of the air passages. There is no inflammation present.

Microscopic sections of the *liver* show the presence of a neoplasm with an extremely varied microscopic appearance. The majority of the tumor is composed of cells possessing oval to spindle-shaped nuclei with very little surrounding cytoplasm. Some of the cells have a few fine fibrils. The cells are uniform in shape and staining reaction. Mitotic figures are not frequent. The tissue has a primitive appearance and lacks any distinctive differentiation. Within this cellular mesenchyme-like tissue there are islands of differentiated cells which are arranged in cords or ducts bearing some similarity to hepatic cells or cells lining the biliary tract. These more differentiated areas, however, lack any organized architectural arrangement. Also within the cellular spindle shaped areas there are islands of osteogenesis with numerous osteoblasts laying down osteoid. There is early calcification of some of the osteoid beams. The neoplasm appears to be expanding and compressing the surrounding hepatic tissue rather than infiltrating or invading it. This has produced some atrophy in the hepatic cords and some fibrosis. There is extramedullary hematopoiesis in the sinusoids of the liver.

Remainder of the autopsy is within normal limits. The brain is not examined.

Diagnosis

1. Teratoma of the liver
2. Atelectasis neonatorum with hyaline membrane disease of the lungs

Comment

Teratomas of the liver in the newborn are very rare. Parmelee[1] states, "Tumors of the liver are seldom discovered in the newborn period." Concerning liver teratomas, Potter[2] states, "These are extremely rare tumors of the liver which, like teratomas in other locations, are composed of elements derived from all three germ layers and contain skin, brain and other tissues foreign to the liver. One bizarre lobulated tumor was removed from a seven-week old child, who was still alive and well at the age of 12 years." Schaffer[3] states, "The liver is the site of primary tumor with the utmost infrequency in the newborn period."

This case is also of value because of the differential diagnosis of jaundice in the newborn, which was considered by the attending pediatrician. In a newborn that develops jaundice the following possibilities should be considered:

1. Rh incompatibility — Mother Rh negative, infant Rh positive, Coombs test positive.
2. ABO incompatibility — Mother group O, infant group A or B.
3. Syphilis — Mother's and infant's serologic test for syphilis positive.
4. Sepsis — Maybe ruptured membranes prior to labor. Maybe con-

taminated delivery or purulent cord. Maybe positive blood culture. The pediatrician in the present case considered sepsis by treating the infant with penicillin and streptomycin.

5. Toxoplasmosis — Rule out with dye test done on infant's blood sent to Minnesota Department of Health Laboratories.

6. Galactosemia — Rule out by presence of reducing substance in infant's urine after infant has drunk milk. If untreated by galactose free diet infant develops progressive liver enlargement, cataracts, mental retardation.

7. Toxins and Drugs — Infant given excess dose of vitamin K, sulfa drugs or tranquilizers.

8. Congenital hemolytic anemia — Rule out by presence of spherocytes in peripheral blood, family history.

9. Hepatitis — Presence of increased serum transaminase.

10. Atresia of bile ducts — Slowly developing increasing jaundice. Bilirubin and urobilin absent in stools. Liver biopsy and operative cholangiogram.[4]

11. Physiologic jaundice — Bilirubin rarely rises above 10 mgm. % except in dehydrated infants.

12. Cytomegalic inclusion disease — Maybe petechia with jaundice and hepatosplenomegaly. Maybe presence of cytomegalic inclusion bodies in desquamated renal epithelial cells obtained by hematoxylin and eosin stain of centrifuged urine.

13. Congenital leukemia — Rule out with bone marrow examination.

14. Neoplasm of the liver.

15. Congenital nonhemolytic jaundice of Gilbert and Criglar Najjar, Family history — Rule out by glucuronyl transferase test.

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A father reports his teen-age son took a job aptitude test and was found to be suited for retirement. — Fletcher Knebel — in Potomac Fever

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Make the most of yourself, for that is all there is of you.—Emerson

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It is easier to be critical than correct.—Disraeli

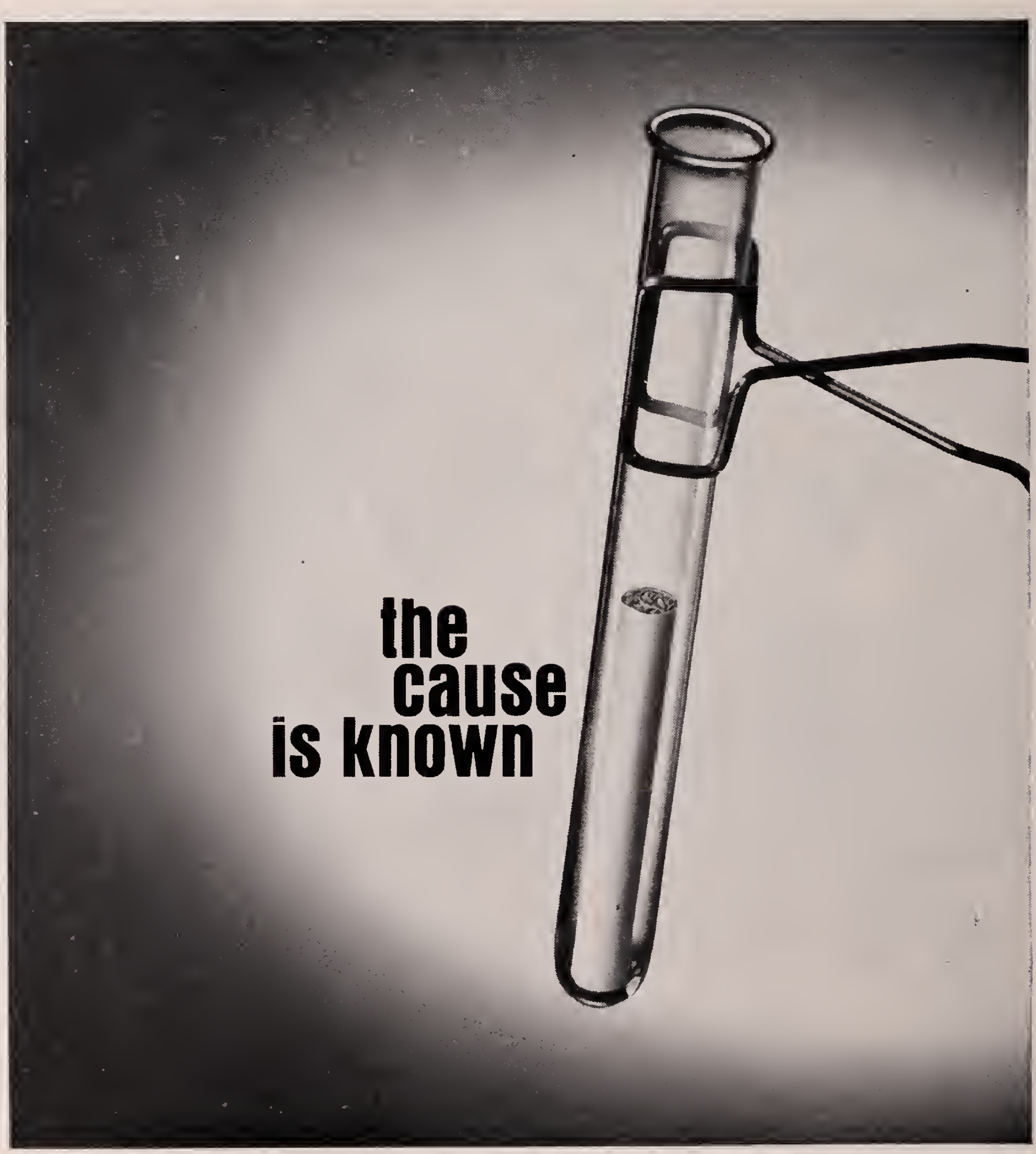
The big question has been answered for many people. The Surgeon-General's report on Smoking and Health gave strong support to overwhelming evidence accumulated by the American Cancer Society over the last 15 years. Cigarette smoking is a major cause of lung cancer.

As the evidence piled up, the Society intensified its public educational efforts, with teen-agers the specific target. Many private and government agencies were stimulated to take action.

But people have short memories. Already the message of the Surgeon-General's report has been blurred with the passage of time. Unless those with the responsibility for protecting health act vigorously, the public will continue to lose sight of the risk...and smoke cigarettes.

We are faced with some compelling questions. How to motivate adults to stop smoking cigarettes? How to influence teen-agers not to start? How to help those who want to stop but can't? *Between us, doctor, we must find the answers.*

american cancer society®



Special Article

Rheumatic Fever

Minnesota Secondary Prevention Program

LAWRENCE V. PERLMAN, M.D.*
JULIUS ELLISON, M.D.**
HERMAN KLEINMAN, M.D.***
DEAN S. FLEMING, M.D.†
Minneapolis, Minnesota

IN 1960, after study that rheumatic fever was still a problem of some magnitude in Minnesota (2,700 new or recurrent cases annually or an approximate attack rate of .73 per 1,000),[1,2] the Minnesota Heart Association, Minnesota State Medical Association, Minnesota State Pharmaceutical Association, and the Minnesota Department of Health established the Rheumatic Fever Secondary Prevention Program. Its purposes were four-fold: establishment of a case registry system by which rheumatic patients are identified and provision is made for automatic patient follow-up; maintenance of rheumatic-fever statistics so that significant trends in this disease may be analysed; dissemination of educational material to patients and physicians; and provision of penicillin or sulfadiazine at reduced cost through local pharmacists.

The Minnesota program is one of many local and statewide programs which have as their purpose the prevention of recurrent rheumatic fever. It is somewhat unusual in that it has no age restrictions (certain states provide service only for those under 21) and no means test (although the program is aimed at the medically indigent), and that it depends upon local physicians for verification of diagnosis (certain states have clinics where diagnoses are checked).[3,4] Both Connecticut and Ohio have similar programs.[5]

All such programs are based on the evidence that individuals with a history of rheumatic fever experiencing Group A, beta hemolytic streptococcal infections, have a total rheumatic fever recurrence rate of 25 to 67 percent, that many of these infections are subclinical, and that continuous penicillin (or sulfadiazine) prophylaxis will reduce this rate by 80 to 90 percent. Moreover, it is speculated that those who recover from their initial attack without evidence of car-

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ditis will probably not develop rheumatic heart disease if maintained on prophylaxis.[6]

The purpose of this report is to record and comment upon statistics compiled in the first four years of operation of the Minnesota Rheumatic Fever Secondary Prevention Program.

Mode of Operation

A patient is registered in the secondary prevention program when his physician makes application (Figure 1) to the Minnesota Department of Health. The Division of Disease Prevention and Control processes these applications and in doubtful cases requests additional information from the referring physician. Prescription pads (four prescriptions, each for a three-month supply) are sent to the physician for patient use.

Following the receipt of the stub of the fourth prescription, the physician is sent a re-application form, and another prescription book is mailed. If a patient is delinquent, as evidenced by failure to fill a prescription for more than four months, his physician is notified by mail. Notification of delinquency is repeated at eight and twelve months. Services of public health nurses are available for follow-up.

Materials and Methods

Statistics were taken from the first 8,604 rheumatic fever program applications (which represent all those patients enrolled from January 27, 1960 to January 27, 1964) and programmed on McBee sort cards. They were then tabulated (See Tables 1 through 9).

Results

Table 1 shows the number of cases registered from January 27, 1960, to January 27, 1964. It will be noted that the number registered per year has fallen from a high of 3,374 during the first year of operation to 1,369 in the fourth year. While the higher figure undoubtedly represents the inclusion of individuals with inactive disease, it is also quite possible that some of this decrease indicates that the incidence of acute rheumatic fever is declining in Minnesota. Between the 1955 and 1958 surveys, rheumatic fever decreased by 15 percent.[1,2]

TABLE 1
Rheumatic Fever Registry Analysis — Number of Cases Registered

	Year 1 Jan. 27, 1960 through Jan. 26, 1961	Year 2 Jan. 27, 1961 through Jan. 26, 1962	Year 3 Jan. 27, 1962 through Jan. 26, 1963	Year 4 Jan. 27, 1963 through Jan. 26, 1964
Year Total	3,374	2,241	1,620	1,369
Cumulative Total	3,374	5,615	7,235	8,604

TABLE 2
Rheumatic Fever Registry Analysis — Groups By Age and Sex

Age Group	Male	Percent of Total	Female	Percent of Total	Total	Percent of Total
0- 4 years	133	3.2%	121	2.7%	254	2.9%
5- 9 years	1,075	26.1%	972	21.7%	2,047	23.8%
10-14 years	1,269	30.8%	1,120	25.0%	2,389	27.8%
15-19 years	574	14.0%	674	15.0%	1,248	14.5%
20-29 years	430	10.5%	679	15.1%	1,109	12.9%
30-39 years	334	8.1%	486	10.8%	820	9.5%
40-49 years	179	4.3%	267	5.9%	446	5.2%
50-over	112	2.7%	138	3.1%	250	2.9%
No Data	11	.3%	30	.7%	41	.5%
Total	4,117	100.0%	4,487	100.0%	8,604	100.0%

PATIENT APPLICATION FORM

MINNESOTA RHEUMATIC FEVER SECONDARY PREVENTION PROGRAM

Minnesota State Medical Association, Minnesota Department of Health,
Minnesota Heart Association, Minnesota State Pharmaceutical Association

Upon receipt of this application form, the Minnesota Department of Health will send you a pad of prescription blanks for a supply of your choice of prophylactic medication, identified by your patient's name and our serial number.

Patient's Name: ______________________ (PLEASE PRINT) Age _____ Sex _____ Race: W ___ N ___ I ___

Patient's Weight: ______________________

Address: ______________________ STREET OR RURAL ROUTE ______________________ CITY, VILLAGE, TOWNSHIP ______________________ COUNTY

Name of Parent or Guardian: ______________________

____

(INFORMATION BELOW FOR STATISTICAL PURPOSES ONLY)

RHEUMATIC FEVER DATA

A. Date of initial onset of Rheumatic Fever: ______________________

B. Check the bases for diagnosis of Rheumatic Fever — any single episode — according to Jones Criteria, MODIFIED — September 1955. ______________________

MAJOR DIAGNOSTIC CRITERIA

________ Carditis

________ Polyarthritis

________ Chorea

________ Subcutaneous Nodules

________ Erythema Marginatum

MINOR DIAGNOSTIC CRITERIA

________ Fever

________ Arthralgia

protein

________ Increased ESR, WBC, or presence of C-Reactive

________ Prolonged PR — Interval on ECG

________ Previous Beta-Hemolytic Strep. Inf.

________ Previous Rheumatic Fever of Inactive Rheumatic Heart Disease.

C. Number of recurrences: ______________________ D. Date of last recurrence: ______________________

____

____

CURRENT DIAGNOSIS

E. Present status of Rheumatic Fever: Active: ______________ Inactive: ______________

F. Rheumatic Heart Disease: Definite: ____________ Suspected: ____________ None: ____________

G. Type of Valvular Lesion: Mitral Insuff: ______________ Mitral Sten: ______________

Aortic Insuff: ______________ Aortic Sten: ______________

H. Other Comment: (Cardiac Surgery, Subacute Bacterial Endocarditis, Decompensation, Arrhythmia, Enlargment, etc. ______

____

____

DRUG PREFERENCE

I. Please check below your choice of drug for this patient:

☐ Oral Penicillin ☐ Injectable Penicillin ☐ Sulfadiazine

Physician's Signature: ______________________ Phone: ______________

Address: Street: ______________________ City: ______________

____

Additional application forms or information on this program may be obtained by writing to: HEART DISEASE CONTROL PROGRAM, Minnesota Department of Health, Minneapolis 14, Minnesota; or by Telephone: FEderal 9-7751.

Fig. 1

Table 2 shows the distribution of individuals with respect to age and sex. Fifty-two percent of the enrollment is female, while the majority of registrants, 82 percent, are under 30 years of age.

Table 3 shows why this is so. Fifty-nine percent of the patients were admitted to the program with a recent onset of rheumatic fever (less than five years). Thirty-one percent were enrolled with acute rheumatic fever existing at the time of registration (Table 4).

Table 5 lists the major and minor diagnostic criteria for inclusion in the program. Of the patients enrolled, 11.8 percent had no major criteria while 8.1 percent had no minor criteria. Patients such as these were enrolled if they had rheumatic heart disease or a history of rheumatic fever. Occasionally patients without major criteria were included in the program if their physician felt that this was the most appropriate diagnosis.

TABLE 3

Rheumatic Fever Registry Analysis
Interval Since Onset

Age Group	Male	Female	Total	Percent of Total
Less than 1 year	1,674	1,509	3,183	37.0%
1 year	338	351	689	8.0%
2-4 years	609	668	1,277	14.8%
5 years or more	1,192	1,592	2,784	32.4%
No Data	304	367	671	7.8%
Total	4,117	4,487	8,604	100.0%

TABLE 4

Rheumatic Fever Registry Analysis
Status of Rheumatic Fever

Status	Male	Female	Total	Percent of Total
Active	1,284	1,405	2,689	31.3%
Inactive or no data	2,833	3,082	5,915	68.7%
Total	4,117	4,487	8,604	100.0%

TABLE 8

Rheumatic Fever Registry Analysis
Drug Preferred

Drug	Total	Percent of Total
Oral Penicillin	7,507	87.2%
Injectable Penicillin	619	7.2%
Sulfadiazine	478	5.6%
Total	8,604	100.0%
Shift from one to other	112	1.3%

Tables 6 and 7 show that 34 percent of the patients enrolled had definite heart disease, while 20 percent had suspected heart disease. Mitral disease (stenosis and insufficiency) was the most commonly reported valvular abnormality.

Table 8 shows the type of medication requested by each participating physician. Oral penicillin is the overwhelming choice.

Table 9 shows those cases officially closed as of January 27, 1964. The chief cause of case closure, "lost to follow-up in some other way," was usually due to the patient's failure to return to his physician. Only 13.5 percent of the total enrolled (those recorded as "lost to follow-up in some other way," those recorded as "moved away," those recorded as "does not wish to continue in program," those recorded as "spiritual healing," and those "not financially able to continue") can actually be regarded as lost to medical care.

Comments and Conclusion

Statistics, such as these, reported by over 1,500 physician observers are open to a large source of error. Rheumatic fever is a notoriously difficult diagnosis to substantiate, particularly with the combination of polyarthritis, fever, leukocytosis, and increased sedimentation rate which may occur in many other conditions.

Two studies seeking to verify the diagnosis of rheumatic fever in Minnesota have given conflicting results.

Accuracy of Diagnoses

In 1959 Rosenfield, checking a sample of 250 cases, found that 90 percent of the diagnoses could be confirmed, but Ellison, analysing the office records of a sample of 388 patients included in this program, could only confirm the presence of major criteria in about 50 percent of the cases.[7,8] However, many physicians do not keep complete records, and, moreover, Ellison did not check hospital records or the records of physicians who may have made the initial diagnosis and then referred the patient to the physician who actually enrolled the patient in the program.

Despite the fact that the percentage of accurate diagnoses is open to question, reporting such data has certain advantages. It offers statistics which may be compared to those of similar programs, and it offers an opportunity to detect certain trends in the incidence and management of rheumatic fever.

As of January 27, 1964, 8,604 patients were enrolled. (Total state population is approximately 3,500,000.) As noted in Tables 2, 3, and 4 the tendency is to include younger patients who have had acute rheumatic fever within two years. While it is true that recurrences are more frequent in the young and those who have had recent acute attacks, the American Heart Association, in the light of current knowledge, recommends indefinite

TABLE 5

Rheumatic Fever Registry Analysis — Major Diagnostic Criteria

Criteria	Male	Percent of Total Male (4,117)	Female	Percent of Total Female (4,487)	Total	Percent of Total (8,604)
Carditis	2,177	52.9%	2,345	52.3%	4,522	52.6%
Polyarthritis	2,899	70.4%	2,993	66.7%	5,892	68.5%
Chorea	185	4.5%	317	7.1%	502	5.8%
Subcutaneous Nodules	180	4.4%	280	6.2%	460	5.3%
Erythema Marginatum	241	5.9%	222	4.9%	463	5.4%
No Data	459	11.2%	552	12.3%	1,011	11.8%
Minor Diagnostic Criteria						
Fever	3,487	84.7%	3,644	81.2%	7,131	82.9%
Arthralgia	2,597	63.1%	2,932	65.3%	5,529	64.3%
Elevated Sed. Rate, Wbc.	3,069	74.5%	3,292	73.4%	6,361	73.9%
ECG Changes	854	20.7%	798	17.8%	1,652	19.2%
Previous Streptococcal Infection	1,535	37.3%	1,676	37.4%	3,211	37.3%
Previous Rheumatic Fever	601	14.6%	762	17.0%	1,363	15.8%
No Data	264	6.4%	430	9.6%	694	8.1%

TABLE 6

Rheumatic Fever Registry Analysis — Rheumatic Heart Disease

	Male	Percent of Total	Female	Percent of Total	Total	Percent of Total
Definite	1,308	31.8%	1,630	36.3%	2,938	34.1%
Suspected	807	19.6%	895	20.0%	1,702	19.8%
None	2,002	48.6%	1,962	43.7%	3,964	46.1%
Total	4,117	100.0%	4,487	100.0%	8,604	100.0%

TABLE 7

Rheumatic Fever Registry Analysis — Valvular Lesions

	Male	Percent of Total Male (4,117)	Female	Percent of Total Female (4,487)	Total	Percent of Total (8,604)
Mitral Stenosis	382	9.3%	627	14.0%	1,009	11.7%
Mitral Insufficiency	711	17.3%	964	21.5%	1,675	19.5%
Aortic Stenosis	103	2.5%	118	2.6%	221	2.6%
Aortic Insufficiency	221	5.4%	184	4.1%	405	4.7%
Other	372	9.0%	481	10.7%	853	9.9%

Continued

prophylaxis. However, the recommendations note that physicians may wish to make exceptions in certain adult patients, particularly those without heart disease. It has recently been recommended that the administration of prophylactic penicillin to adults over 21 be a matter of individual decision depending on the clinical state of the patient, but this involves a certain calculated risk because of danger of rheumatic recurrences in individuals with heart disease.[9]

Polyarthritis

Polyarthritis was the most common major criterion and was noted in 68 percent of the applications, while carditis was listed in 53 percent, and chorea, subcutaneous nodules, and erythema marginatum were each noted in between 5 and 6 percent of the total. This occurrence of major criteria is similar to that noted in the series of Massell et al. (which is representative of many hospital series), except for our incidence of chorea which is 20 percent less.[10]

TABLE 9

Rheumatic Fever Registry Analysis
Cases Closed as of January 27, 1964

		Number	Percent of Total
Died		100	5.6%
Secondary to Rheumatic Fever	40		
General Causes Not Rheumatic Fever	25		
Cause Unknown	35		
*Moved Away		356	19.8%
Taken Off Prophylaxis by Doctor		355	19.8%
Not Rheumatic Fever	17		
Other Reasons or Not Stated	338		
*Lost to Follow-up in Some Other Way (Includes 348 no prescriptions received in over 1 year)		714	39.7%
Allergies		25	1.4%
Not Eligible for Program		84	4.6%
Buying Own Medication	77		
On Welfare	3		
On ADC	4		
Getting Drugs Elsewhere		39	2.2%
*Spiritual Healing		1	.1%
Miscellaneous		123	6.8%
*Patient or Family Does Not Wish to Continue in Program	90		
In Military Service	18		
Being Followed by Hospitals	7		
Taking Drugs Not Offered in Program	6		
*Not Able Financially to Continue	1		
Developed Leukemia	1		
Total		1,797	100.0%

*May be considered lost to medical follow-up.

Prophylaxis

Oral penicillin was the overwhelming choice for prophylaxis. Certain well-controlled studies have shown that intramuscular bicillin is the most effective means of preventing recurrent rheumatic fever, possibly because the dose of bicillin is bactericidal and because a patient is assured of getting his medicine if given by injection. Oral penicillin is the means of prophylaxis in 88 percent of cases. The preference for this drug is probably explained by its lack of toxicity, its ease of administration, and its degree of patient acceptance.[11]

Provision of continuing care is a major problem in the control of rheumatic fever. In the Minnesota program, after four years of operation, 1,797 of the total of 8,604 cases enrolled had been shifted from the active registry to the closed file. Of these closed cases, 1,162 could be considered lost to medical follow-up and 378 had been referred to public health nurses. While this figure of 1,797 does not take into account those who are delinquent for periods of less than a year, the small percentage lost to medical follow-up speaks well for the registry system.

The Minnesota Rheumatic Fever Program provides low-cost medication, the maintenance of a medical registry, the collection of rheumatic fever statistics, and the dissemination of professional and patient educational material.

Over half of those enrolled had either definite or suspected rheumatic heart disease. The mitral valve was most commonly affected.

Acknowledgements

The authors wish to acknowledge the assistance of Dr. Lewis Wannamaker, Professor of Pediatrics, University of Minnesota, who reviewed the manuscript.

Part II — "Recurrences" will appear in January issue.

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Rules for this contest are in Minnesota Medicine 47:956, 1964.

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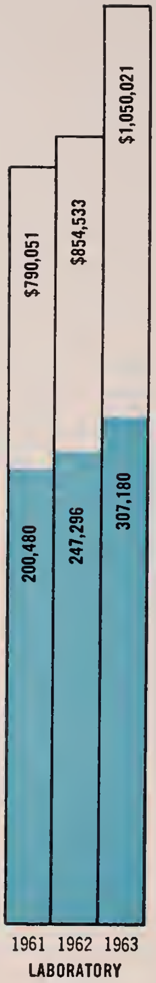
Worry is like a rocking chair — it will give you something to do but it won't get you anywhere.— Audiogram



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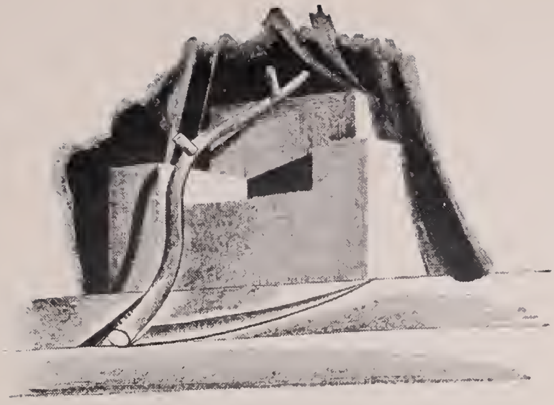

In Memoriam

Death to a good man is but passing through a dark entry out of one little dusky room of his father's house into another that is fair and large, lightsome and glorious and divinely entertaining.—Clarke

DAVID ELLISON

Dr. David E. Ellison, retired Minneapolis physician and former president of the Twin City Rapid Transit Co., died November 6th. He was 72. Born in Minneapolis, Dr. Ellison graduated from the University of Illinois Medical School.

He was a past board member and director of Adath Jeshurun synagogue, a member of the American Medical Association, and associate member of the Hennepin County Medical Society and Minnesota State Medical Association.

He is survived by his two sons, Dr. Ellis Ellison of San Mateo, California and Dr. Evan Ellison of Minneapolis, and a daughter.

EARL R. LOWE

Dr. Earl R. Lowe, 68, long-time South St. Paul physician and surgeon, died October 22nd in Miller hospital. Born in Hadley, Minnesota, Dr. Lowe received his medical degree from the University of Minnesota.

He had been chief of staff at Riverview Memorial hospital, and was a staff member at St. Luke's and Divine Redeemer hospitals. Dr. Lowe was also a director of the Armour & Co. medical department, a member of the Ramsey County Medical Society, Minnesota State Medical Association and the American Medical Association. He was also a member of the American and Ramsey County Association of Industrial Physicians and Surgeons.

He is survived by his wife, two daughters, two step-daughters, one son, Dr. Alex Lowe of South St. Paul, and two step-sons.

CARLOS W. del PLAINE

Dr. Carlos del Plaine, 71, Minneapolis physician, died October 3rd. Born in Mexico, Dr. del Plaine lived in Minneapolis for forty-two years. He was a graduate of the University of Minnesota School of Engineering and School of Medicine.

Dr. del Plaine had been a member of the staffs of St. Barnabas and Northwestern hospitals, and was a member of the Hennepin County Medical Society, Minnesota State Medical Association and the American Medical Association.

He is survived by his wife and a son.

ARTHUR T. LAIRD

Dr. Arthur T. Laird, 91, a national pioneer in the field of tuberculosis control and superintendent of the Nopeming Sanatorium for more than thirty years, died October 17th, in a Duluth hospital. A native of Madison, Ohio, Dr. Laird was graduated from Oberlin College and the University of Pennsylvania Medical School.

He was a member of the Duluth Chamber of Commerce, St. Louis County Historical Society, American Thoracic Society, American Hospital Association, American Medical Association, and St. Louis County Medical Society. He was a life and 50 Club member of the Minnesota State Medical Association plus membership in various public health organizations.

Dr. Laird was one of the organizers of the first curriculum in the nation for the degree of registered record librarian (RRL).

He is survived by his wife and a step-son.

ANNOUNCING

THE TWENTY-EIGHTH ANNUAL MEETING
of
THE NEW ORLEANS GRADUATE MEDICAL ASSEMBLY

Conference Headquarters — Roosevelt Hotel

March 8, 9, 10, 11, 1965

GUEST SPEAKERS

James E. Eckenhoff, M.D., Philadelphia, Pa.—*Anesthesiology*
A. W. Martin Marino, Jr., M.D., Brooklyn, N. Y.—*Colon and Rectal Surgery*
Wiley Mitchell Sams, M.D., Miami, Fla.—*Dermatology*
Maurice L. Kelley, Jr., M.D., Rochester, N. Y.—*Gastroenterology*
Robert I. Wise, M.D., Philadelphia, Pa.—*General Practice*
Curtis J. Lund, M.D., Rochester, N. Y.—*Gynecology*
S. Gilbert Blount, M.D., Denver, Colo.—*Internal Medicine*
Jerome W. Conn, M.D., Ann Arbor, Mich.—*Internal Medicine*
Francis Murphey, M.D., Memphis, Tenn.—*Neurologic Surgery*
Bayard Carter, M.D., Durham, N. C.—*Obstetrics*
William F. Hughes, M.D., Chicago, Ill.—*Ophthalmology*
Milton S. Thompson, M.D., San Antonio, Tex.—*Orthopedic Surgery*
Benjamin Castleman, M.D., Boston, Mass.—*Pathology*
Harry C. Shirkey, M.D., Birmingham, Ala.—*Pediatrics*
Richard H. Marshak, M.D., New York, N. Y.—*Radiology*
Warren H. Cole, M.D., Chicago, Ill.—*Surgery*
Preston A. Wade, M.D., New York, N. Y.—*Surgery*
Robert Lich, Jr., M.D., Louisville, Ky.—*Urology*

Additional Speaker to be Announced

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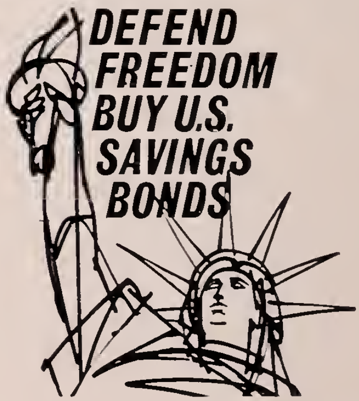

Meetings and Announcements

He that is not open to conviction, is not qualified for discussion.—Whately

DECEMBER

Minnesota Society for Crippled Children and Adults, Inc., (Planning Rehab. Services for Mentally Ill and Mentally Retarded) 9:00 a.m. to 4:30 p.m., Ambassador Hotel, Minneapolis, December 16.

St. Louis County Medical Society, Dinner Dance — 7:00 p.m., Kitchi-Gammi Club, Duluth, December 19.

Ramsey County Medical Society, 8:00 p.m., 15th Floor Lowry Medical Arts Building, St. Paul, December 28.

Academy of Psychoanalysis, New York, December. Sec.: Alfred H. Rifkin, M.D., Academy of Psychoanalysis, 125 E 65th St., New York 21.

JANUARY, 1965

Second Annual American Therapeutic Society-Minnesota Heart Association Symposium, Radisson Hotel, Minneapolis, January 9-10. Subject will be "Therapy of Peripheral Vascular and Cerebral Vascular Disease." Contact: Robert Tuttle, 1821 University Avenue, St. Paul.

Ramsey County Chapter of Minnesota Academy of General Practice, and Ramsey County Medical Society Symposium on "Obesity — Dangers of a Well Fed Population," Lowry Hotel, January 18, in St. Paul. Contact: Charles J. Beck, M.D., 2579 East 7th Avenue, North St. Paul.

Hennepin County Psychiatric Society, 6:30 p.m., Leamington Hotel, Minneapolis, January 4.

Zumbro Valley Medical Society, (Regular meeting and new officers take assignments) 8:00 p.m., Plummer Hall, Rochester, January 6.

Minnesota Academy of Medicine, (Regular meeting) 7:00 p.m. — Town & Country Club, St. Paul, January 8.

St. Louis County Medical Society, Executive Comm. — 6:00 p.m., St. Mary's Hospital, Duluth, January 14. Annual Meeting — 8:00 p.m., St. Mary's Hospital, Duluth.

Ramsey County Medical Society, Lederle Symposium, Lowry Hotel, St. Paul, January 18.

Ramsey County Medical Society, Annual Meeting & Program — 8:00 p.m., 15th Floor Lowry Medical Arts Bldg., St. Paul, January 25.

American Academy of Orthopaedic Surgeons (members and invited guests only), Americana Hotel, New York, January 9-14. Exec. Sec.: John K. Hart, 29 E. Madison, Chicago 2.

American College of Surgeons (sectional meeting), Atlanta Biltmore Hotel, Atlanta, January 25-27. Sec.: Samuel P. Harbison, M.D., 55 E. Erie, Chicago 11.

American Society for Surgery of the Hand, Americana Hotel, New York, January 8-9. Exec. Sec.: Don L. Eyler, M.D., 1919 Hayes St., Nashville 4, Tenn.

Orthopaedic Research Society, Americana Hotel, New York, January 8-9. Sec.-Treas.: R. A. Calandruccio, M.D., 869 Madison Ave., Memphis, Tenn.

Society for Adolescent Psychiatry, New York Academy of Sciences, New York, January 13. Sec.: Frederick J. Wertz, M.D., 30 E. End Ave., New York 10028.

Society of Thoracic Surgeons, Chase-Park Plaza Hotel, St. Louis, January 25-27. Sec.: F. X. Byron, M.D., City of Hope Medical Center, 1500 Duarte Rd., Duarte, Calif.

Southern Radiological Conference, Grand Hotel, Point Clear, Ala., January 29-31. Sec.-Treas.: Marshall Eskridge, M.D., P.O. Box 4097, Mobile, Ala.

ANNOUNCEMENT

Applications for the Part I (written) examination to be given on July 2, 1965, will be accepted in the office of the Secretary during the months of January and February. All applications postmarked after February 28th will be returned to the sender. Application forms and Bulletins of the Board may be obtained by writing to the office of the Secretary, — Clyde L. Randall, M.D., American Board of Obstetrics and Gynecology, 100 Meadow Road, Buffalo, New York 14216.

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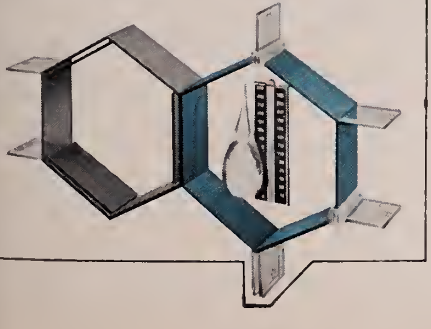

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CONTRAINDICATION: Anuria.

1. Steigmann, F., and Griffin, R.: Evaluation of Quinethazone, a New Diuretic. J. Amer. Geriat. Soc. 11:945 (Oct.) 1963.

2. Schwartz, M.: Office Evaluation of a New Diuretic in Patients with Hypertensive Diseases. Scientific Exhibit Presented at the Clinical Meeting of the American Medical Association, Los Angeles, California, Nov. 25-28, 1962.

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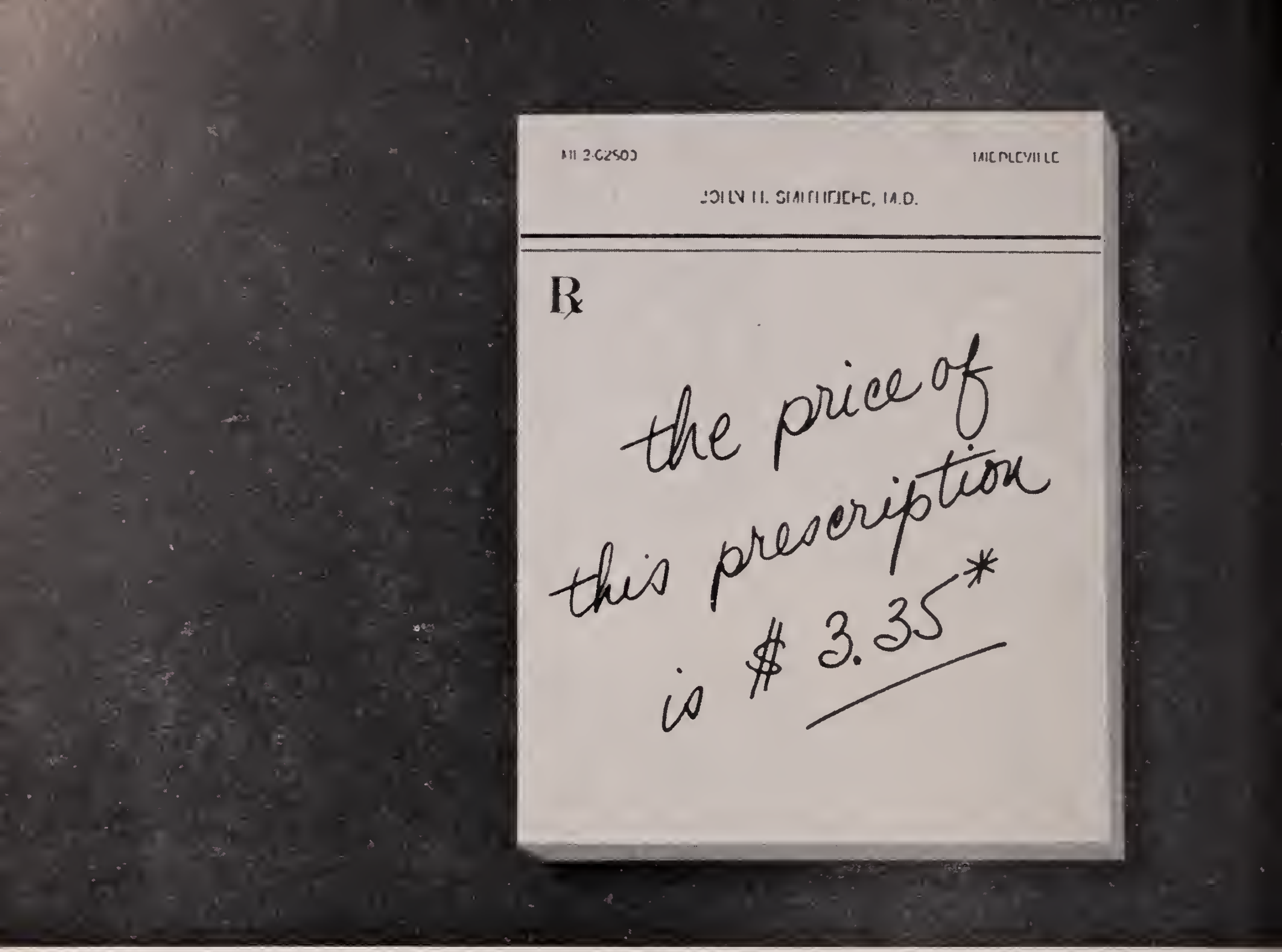

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*Average prescription price, 1963. National Prescription Audit, R.A. Gosselin, Dedham, Mass.

History of Medicine

IN WRIGHT COUNTY, Part XII

JOHN J. CATLIN, M.D.
Buffalo, Minnesota

ROBERT ROSENTHAL, M.D.
St. Paul, Minnesota

Editors Note: Article continued from June 1964 issue of Minnesota Medicine.

Alexander Ridgway, first practiced in 1894 and then was listed as practicing in Annandale in 1896. He was there only a short time and moved to South Haven. Later he was in Belgrade, Stearns County, from where he returned to Wright County to practice in Clearwater. From Clearwater he came to South Haven. This time he stayed there a long period; he was mayor of the town for several terms e. g. in 1935.

Dr. Ridgway was born July 28, 1855 near Columbus, Wisconsin, the son of Joseph and Margaret (Phillips) Ridgway; both parents were born in Cheshire, England, from where they came to Wisconsin and settled on a farm near Columbus. Dr. Ridgway was one of four sons and two daughters. Three sons became physicians — Alexander, Joseph and Alfred M. — and one became a dentist. Joseph practiced in Minneapolis and Alfred M. in Annandale, the dentist in Gainsford. The sisters were Mary and Martha. He had his preliminary education at Columbus, Wis., attended Hamline College and received his medical degree from the College of Physicians and Surgeons, Minneapolis, in 1894; in the same year he received his license. He married Lena Hanson of Minneapolis in July 1896. He died of chronic mitral insufficiency and arteriosclerosis on April 3, 1937 at South Haven at the age of eighty-one and was survived by his wife, one son, Russell, of Minneapolis and one daughter, Mabel, of South Haven.

Dr. Ridgway was a member of the Minnesota State Medical Society, the Stearns-Benton County Medical Society, the Woodmen and Royal Neighbor Lodges.

It seems he was a "floater," changing his location rather frequently and apparently was not too successful in establishing a very good practice. It seems he was a fine person, known for his exemplary habits.

Alfred Miller Ridgway, opened his practice in Annandale in July of 1890, shortly after his graduation and has remained there since. Dr. Ridgway, like his brother Alexander, was born in Dodge County, Wisconsin on his parents' farm near Columbus January 29, 1863. In 1882 he went to Minneapolis and worked for a while as a fireman for a railroad and from 1880 to 1885 he worked as clerk in a drugstore. In 1886 he opened a real estate office and earned enough to go to college. Later he studied at the School of Medicine of the University of Minnesota and graduated in 1890. After an internship at the Minneapolis General Hospital* he located in Annandale where he continued to practice until his death in 1950 — almost sixty

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*He had an appointment as government surgeon at Fort Totten, near Devils Lake, North Dakota, but after inspecting the place he refused to accept it.

Continued

years.* He had a well grounded medical education, good common sense and a genial disposition, which made him a very successful country doctor and a credit to his profession. He kept fine horses (six in the summer and eight in the winter) and equipment and he had the proper physique to withstand the irregular hours and the vagaries of the Minnesota weather until he was past eighty. The area he covered extended from Rockford to Watkins and from St. Cloud to Cokato.

Early in his career he bought a one cylinder chain-drive machine. When he used it out of town he always made sure that the team came after him. After he got rid of this auto he used horses again for two years. He was a good diagnostician — without the help of present-day laboratory facilities. He had the gift to inspire confidence in his patients and their families. Many considered him one of the ablest and best known country doctors in Minnesota. For many years he was local surgeon for the Soo Line and his honesty and capability made for quick settlements in injury cases. His appointment to this Railroad came about in the early years of his practice. When a railroad wreck occurred on the Soo Line near Maple Lake during the State Fair week, he brought thirty-two of the injured to Annandale. The Soo Line was so pleased with his work that they offered him the position. He held it for forty years.

When the Wright County Medical Society was reorganized under this new name August 1, 1894 at the American House in Buffalo, he called the meeting to order. He was again a charter member when the society was reorganized a second time in 1903.

It has been mentioned there were four brothers and two sisters, and two of the brothers were physicians and one a dentist. He, like his brothers, had his preliminary education in Columbus, Wis., and then worked on the farm. He entered the University of Minnesota in 1887. In 1895 he took some postgraduate work in New York, in 1900 in Chicago and at one time in Baltimore. He was licensed in June, 1890. He also was licensed to practice in North Dakota September 20, 1902. He married Viola Ponsford, daughter of William and Mary (Townsend) Ponsford, of Corinna Township, Wright County. She had been a schoolteacher. They had no children.

Dr. Ridgway was very active in medical and civic affairs. He attended the meetings of the Wright County Medical Society regularly, was a member of the Minnesota State Medical Society (a member of its fifty year Club) and the A.M.A., also of the Southern Minnesota Medical Association, and the Northern Minnesota Medical Association and the American Association of Railway Surgeons. He was director of the State Bank at Annandale, president of the village council for many terms and village health officer. He was an enthusiastic supporter of the electric light project and had a great financial interest in the Annandale Electric Light and Power Company. He owned much real estate. He was a Mason and an Odd Fellow. He was a member of the Methodist church and very strict in his habits — no drinking, smoking or profanity.

In June, 1940, Annandale honored this important citizen with "Ridgway Day" (June 14). He had been physician of this town fifty years and had delivered more than 3,500 babies, beginning at a time when the roads were too bad for driving so that he often had to walk. The whole town turned out to honor him; there was a pageant in costumes and songs depicting the five decades.

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*He interned at the Minneapolis General Hospital while he was still at college. He may have practiced for a very short time in Eden Valley, Meeker-Stearns County, in 1899.

He died May 19, 1952 at the age of almost ninety from coronary insufficiency and bronchopneumonia.*

Albert Parker Rounsevelle, apparently moved to Delano at the very end of 1878 as his professional card began to appear on January 2, 1879. "A. P. Rounsevelle, M.D., Physician and Surgeon. Office in Eppel Building next door to hardware store. Can be found at his office Wednesdays and Saturdays from 1 to 4 o'clock p.m."** This may indicate that he practiced certain days in other towns. Very soon he sublet his office (or part of it) to the Woodburn Brothers, dentists of Minneapolis, who came to Delano the last week of every month for some time. Early in 1880 he had moved his office to the corner of River Street and Railroad Ave. It seems he was a fairly active practitioner at that time. He became interested in the organization of the Village improvement association. In February, 1880 he cared for Dr. Flannigan's patients, during the fatal illness of the latter's wife. When Dr. Cady needed assistance in a difficult case in Maple Lake and Dr. Catlin was absent, Dr. Rounsevelle was called.

About May 1, 1882 he moved to Grand Forks joining, for a short time, Dr. Scott. When he left Delano the newspaper noted that during his short stay he proved himself "a first class physician and good citizen." It seems he did not remain long in Fergus Falls because late in 1888 a news item states that for the past five years he had resided in Larrimore, Dakota. He therefore must have come there in 1883. He was a charter member of the Inter-County Medical Society of North Dakota*** when it was organized in the winter of 1899 at Northwood, Grand Forks County.

He may have returned for a short time to Delano as he is listed there in 1900 as one of three physicians in that town — the other two being Drs. J. T. Catlin and John Shrader, although this is not too likely as at this time he was at the height of his activity in North Dakota.

Dr. Rounsevelle was born August 16, 1845† on a farm in Thomkin County, New York, a descendent of one of the oldest colonial families. He lived on a farm until he was nineteen years old and then enlisted in the Union Army and served in Company F of the 185th New York Volunteer Infantry. He participated in the Grand Review in Washington May 31, 1865. After the war he completed a course at Courtlandville Academy and then studied medicine, graduating from Philadelphia College in 1871 and later on from Rush Medical College. He supposedly started to practice in 1871.

Dr. Rounsevelle remained in Larrimore for twenty-eight years. He lived to be one of the oldest pioneer physicians of North Dakota and earned a high reputation. He was surgeon for the Great Northern Railway over twenty years and County coroner for a similar period. He was very active in the North Dakota Medical Society, was its treasurer from 1889 to 1891 and its president in 1893. In 1910 he moved to Florida. He settled on a ten acre grove at Lemon City in the suburbs of Miami; and died there many years later.

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*His obituary appeared in Minnesota Medicine, June, 1952.

**The Eagle (Delano), January 2, 1879.

***This was the first medical society in the Red River Valley outside of Fargo.

†Much of the following is taken from "North Dakota Medicine, Sketches and Abstracts" by J. Grassick, M.D., 1926 pp. 85-86.

Continued

Dr. J. (Jacob) Ryder is mentioned in the *Wright County Eagle** as having located in St. Michael in the summer of 1880. He was considered a satisfactory physician but he stayed only a little over one and one-half years,** leaving St. Michael without a physician.

He is probably identical with Dr. Jacob Rider who was licensed in Minnesota by exemption, November 26, 1883 and located in Cologne, Carver County, in that or the following year. He was much interested in real estate and for that reason moved to St. Paul in 1887. In 1890 he lived in Albany, Stearns County, and later returned to Cologne.*** He was considered an able physician. He was born in 1843 and died in 1895.

James Mansfield Ryder, a homeopath, came to Buffalo in 1889. He apparently did not stay long in Wright County and moved to California; after about a year there he moved to McCoy, Oregon where he died of apoplexy May 29, 1900.

Dr. Ryder was born in Clyde, New York, in September, 1822 and came to Milton Township, Dodge County in 1855 and was mainly interested in farming, but also practiced medicine. Nothing is known of his medical education and he was not licensed to practice in Minnesota. In Oregon he was affectionately known as "Uncle Tim" Ryder, but he was not licensed there either.†

Edward A. Shannon, practiced in Buffalo in 1886 but may have come there years before. In 1888 he located in Watertown, Carver County and was coroner there in 1891 and 1892.‡ In 1892 he returned to Wright County, locating in Buffalo, and remained there until 1905 when he apparently moved to Bemidji, Beltrami County.

Dr. Shannon graduated from the St. Paul Medical College in 1886 and was licensed April 22, 1886. He is remembered as a kind-hearted, honest and sincere practitioner, but somehow seemed to lack the faculty to inspire confidence in his patients. Some think the reason was the lack of postgraduate education. He was a thin man of medium height and wore a chin beard. He was respected as a civic-minded man.

He was a charter member of Wright County Medical Society when it was reorganized under this new name in 1894. In 1903 he was elected Secretary of the Society when it was again reorganized. It seems he was very active in the Society and in 1904 read a paper on "Some Points in the Diagnosis of Stomach Cancer."

Dr. Shannon died on January 17, 1927.

E. F. Schleig, located in Watertown, Carver County in July, 1886. It seems he saw patients frequently in Wright County, and from the start his card appeared in the *Delano Eagle* and it is probable that he came to Delano on regular visits. Immediately after his arrival in Watertown he was appointed health officer to fill Dr. J. H. Franks' unexpired term. In December, 1886 he moved to Minneapolis, but his professional card continued in the *Delano Eagle*. In February, 1887 he was the guest of honor at the Hotel de Young and in March a news item# reads, "Dr. Schleig of

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*The Wright Co. Eagle, June 24, 1880.

**The Wright Co. Eagle, April 24, 1882.

***A History of Medicine in Scott and Carver Counties, Minnesota Medicine, July, 1948, p. 800.

†Charles E. Bigelow "History of Medicine in Dodge County," Minnesota Medicine, July, 1943, p. 632 and August, 1943, p. 722.

‡History of Medicine in Scott and Carver Counties, Minnesota Medicine, July, 1948, p. 801.

#Delano Eagle, March 24, 1887.

Minneapolis paid his customary visit to Delano this week. He avers that his practice here is on the increase." He spent Christmas of that year in Delano.

Dr. Schleig was graduated from a German and an American college, but nothing is known of his background or his later years.

John Strickler Shrader, practiced in Delano for fifteen years. He was born in Niagara County, New York, March 9, 1858 and received his preliminary education at Clarence Academy in New York. He graduated from the Medical Department of the University of Michigan in 1885. He practiced in Hadley, Michigan six months and then came to Delano in 1886. He was licensed in Minnesota September 7, 1886. In that year he and Dr. T. J. Catlin were the only physicians listed in Delano; in 1890 he was one of three (the other two being Drs. Catlin and Rounsevelle). In 1901 he took postgraduate work in Vienna, Berlin, Paris and London and then located in Springfield, Brown County, in partnership with Dr. C. J. Rothenberg, where he practiced until 1932.

This must have been a restless period as he resided for short periods in Wheaton, Traverse County (1932) ; Glenville, Freeborn County (1932) ; Hollandale, Freeborn County (1933) ; Jordan, Scott County (1935) and apparently also in Marietta, Lac qui Parle County. Early in 1940 he retired to Springfield, but in 1943 he was in Lamberton, Redwood County. He died July 5, 1945 at Lamberton from acute cardiac dilation at the age of eighty-eight.

While in Wright County he was a member of the Pension Board, holding meetings in Buffalo. Dr. Shrader was a husky, muscular, nice appearing and genial gentleman, and a good, hard working general practitioner, while at Delano. He could stand the rigors of the climate, and the long irregular hours.

In March, 1887 the following story about him appeared in the newspaper.* "Dr. Shrader has concluded since last Sunday that the only serviceable vehicle with which he can successfully prosecute his calling is a pair of Norwegian snow-shoes. Had to abandon his cutter on a trip to Lake Sarah — finished with a pair of homemade Norwegian skiis. Has been practicing since."

For several years he was a member of the State Board of Medical Examiners. He may have been coroner in 1887 as he held an inquest in October in Frankfort where a man had injured himself accidentally, and in November went to Watertown with Dr. T. J. Catlin and a lawyer to meet with the Coroner of Carver County for the purpose of exhuming a woman to determine the cause of death. In December we read again of an autopsy in a supposed case of murder in which Dr. Shrader assisted. Another inquest was held by him in January, 1888.**

In September, 1888 he left Delano and located in Black River Falls, Wisconsin, but at the end of October he was back in Delano. He apparently resumed coroner's duties, as in December, 1889 he did a chemical examination of a loaf of bread in a case of a suspected murder attempt; he found a large amount of arsenic.*** In the same year the newspapers reported that he performed a difficult operation on a woman — the removal of a tumor

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*Delano Eagle, March 3, 1887.

**Delano Eagle, October 13, 1887, November 24, 1887, December 1, 1887, January 12, 1888.

***Delano Eagle, December 12, 1889.

Continued

from the neck. The story says that Minneapolis doctors had claimed that it could not be removed successfully.*

Dr. J. J. Catlin remembers him in the mid 90's. At that time it was the custom for boys to shoot cannons, ring bells or blow steam whistles after midnight July 3 to celebrate the 4th. Some of the boys, including Dr. Catlin, at the age of fifteen, rang the school bell. The school being near Dr. Shrader's home, he finally could not stand it any longer and came out barefoot to chase the culprits. He was well liked in the area around Delano.

Dr. Shrader was a charter member of the Wright County Medical Society when it reorganized under this new name in 1894.

A. R. Smith, in May, 1881, after the arrival of Dr. S. R. Wakefield in Monticello, a new item states "Monticello has now 3 doctors: Gibbs, Wakefield and Smith. . . . "** And there is one more notice about him which does not speak too well of him: "A Dr. A. R. Smith of Monticello has been traveling through the town trying to make people believe he can cure consumption.***" Nothing more is known about him.

John Elford Soper, was in Delano from 1896 to 1899. He was born in England and came to America when a young man. He had been quite an athlete and a boxer in England.

He graduated from the University of Minnesota College of Medicine in 1896 and came to Delano in the same year. In June, 1899 he moved to Norwood, Carver County,† and later to Minneapolis, where he practiced many years. He served in World War I with the 151st Artillery Medical Corps. He was chairman of the National Cemetery Association and was active in helping get the Federal grant for the establishment of Fort Snelling National Cemetery. He was the first commander of the Theodore Peterson American Legion Post in Minneapolis.

Dr. Soper came to Delano single, but that summer he married Miss Mildred E. Lawrence of Minneapolis. There was a big wedding parade from downtown Delano to their new home up Third Street. He died in Minneapolis, March, 1956 at the age of eighty-nine years. A long life of service for a medical man of the horse and buggy days.

To Be Continued

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*Delano Eagle, January 10, 1889.
**The Wright County Eagle, May 21, 1881.
***The Wright County Eagle, July 1, 1881.
†See "History of Medicine of Scott and Carver Counties," Minnesota Medicine, July, 1948.

Life is like a camel. You can make it do anything except back up.—Marcelene Cox

Blessed is the man who having nothing to say, abstains from giving us wordy evidence of the fact.—George Eliot

A

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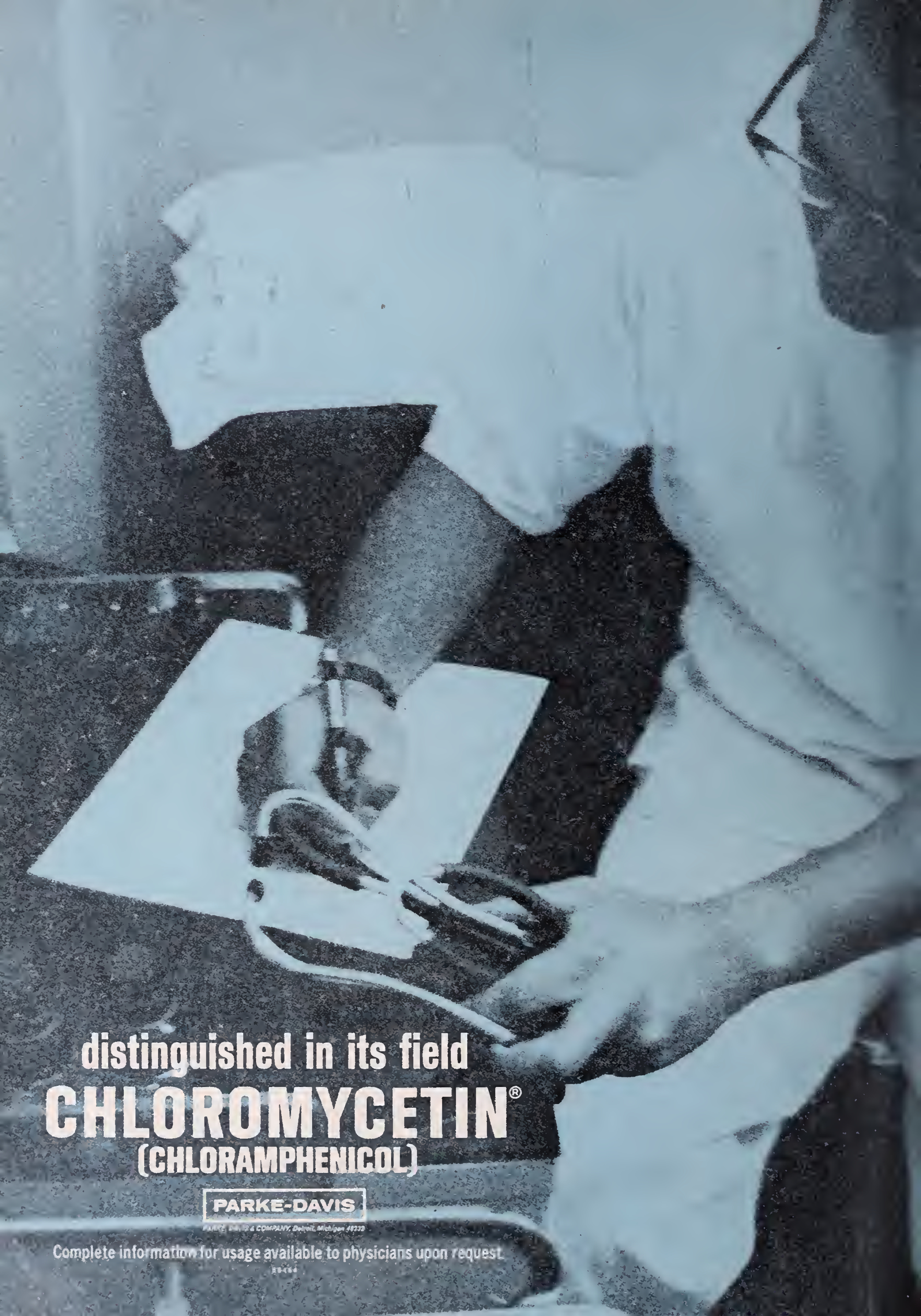

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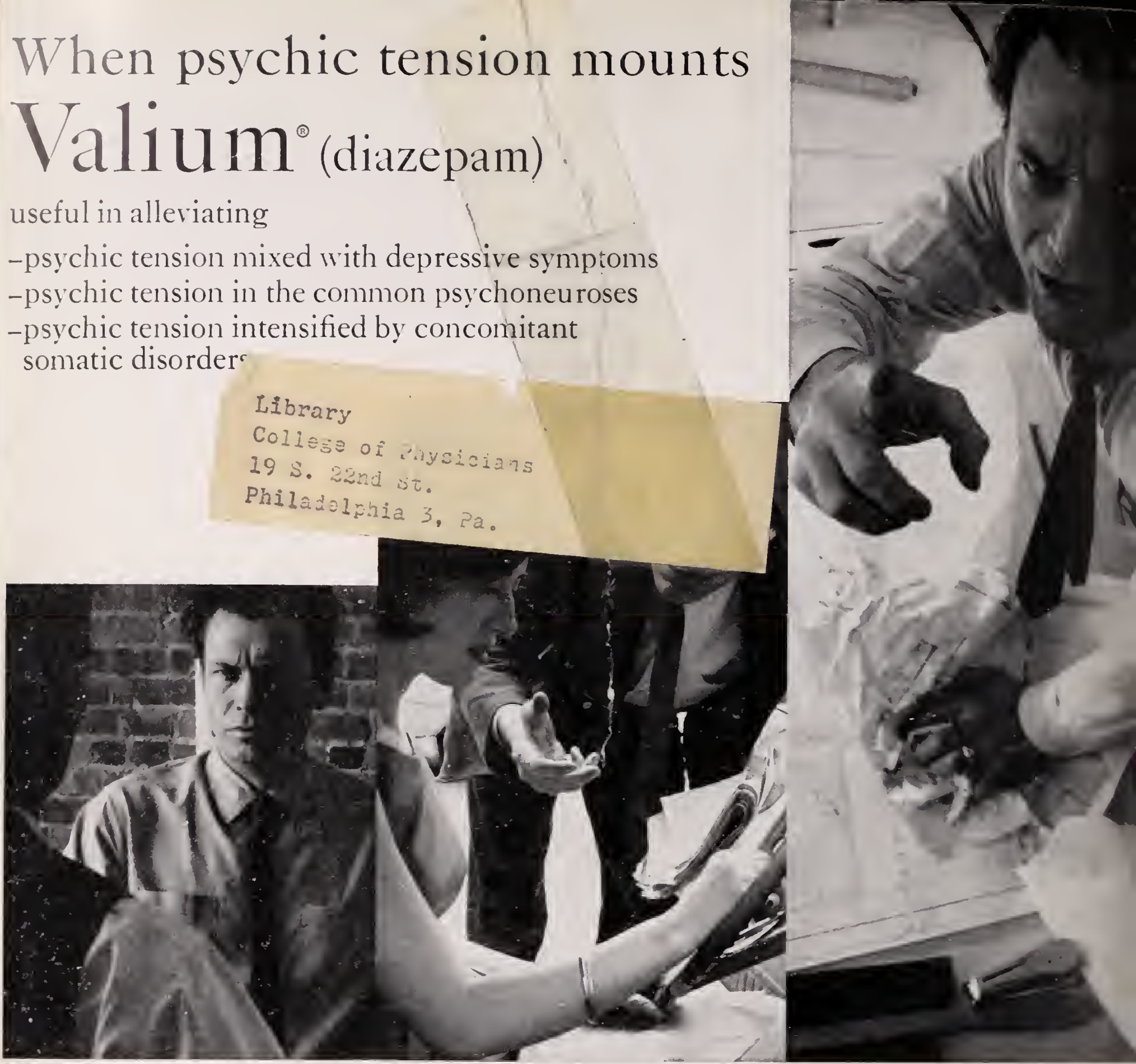

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Dosage and administration	*Usual daily dose*
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Alcoholism: As an aid in symptomatic relief of acute agitation, tremor, impending or acute delirium tremens and hallucinosis	10 mg, 3 or 4 times during the first 24 hours; reducing to 5 mg, 3 or 4 times daily as needed
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Warning: Valium (diazepam) is not of value in the treatment of psychotic patients, and for this reason should not be employed in lieu of appropriate treatment.

Precautions: In elderly or debilitated patients, it is important to limit the dosage to the smallest effective amount to preclude the development of ataxia or oversedation (not more than 1 mg, 1 or 2 times daily initially, to be increased gradually as needed and tolerated). As is true of all CNS-acting drugs, until the correct maintenance dosage is established, patients receiving Valium (diazepam) should be advised against possibly hazardous procedures requiring complete mental alertness or physical coordination. Driving an automobile during the period of Valium (diazepam) therapy is not recommended. In general, the concurrent administration of Valium (diazepam) and other psychotropic agents is not recommended. If such combination therapy is used, careful consideration should be given to the pharmacology of the agents to be employed with Valium (diazepam)—particularly with known compounds which may potentiate the action of Valium (diazepam), such as phenothiazines, barbiturates, MAO inhibitors and other antidepressants.

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